A COMPARATIVE STUDY OF INTRAVENOUS LABETALOL WITH ORAL ANTIHYPERTENSIVE COMBINATION NIFEDIPINE AND ALPHAMETHYLDOPA IN THE ACUTE PREOPERATIVE MANAGEMENT OF HIGH BLOOD PRESSURE IN SEVERE PREGNANCY INDUCED HYPERTENSION PATIENTS.

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY
BRANCH X

DEPARTMENT OF ANAESTHESIOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI - 600 003.

MARCH 2008

CERTIFICATE

This is to certify that the dissertation entitled, ***"A COMPARATIVE STUDY OF INTRAVENOUS LABETALOL WITH ORAL ANTIHYPERTENSIVE COMBINATION NIFEDIPINE AND ALPHAMETHYLDOPA IN THE ACUTE PREOPERATIVE MANAGEMENT OF HIGH BLOOD PRESSURE IN SEVERE PREGNANCY INDUCED HYPERTENSION PATIENTS"*** *submitted by Dr.SUDHAKAR.R , in partial fulfillment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Department of Anaesthesiology, Madras Medical College, during the academic year 2006 – 2008.*

DR.T.P.KALANITI, M.D.,
DEAN,
MADRAS MEDICAL COLLEGE &
GOVT. GENERAL HOSPITAL,
CHENNAI – 600 003.

PROF.S.GAYATHRI,M.D.,D.A
PROFESSOR & H.O.D,
DEPT OF ANAESTHESIOLOGY,
MADRAS MEDICAL COLLEGE,
CHENNAI – 600 003.

ACKNOWLEDGEMENT

I am extremely thankful to **Dr.T.P.Kalaniti, M.D**., Dean, Madras Medical College,for his kind permission to carry out this study.

I am immensely grateful to **Prof.Dr.S.Gayathri , M.D.,D.A**., Professor and Head of the Department, Department of Anaesthesiology, for her concern and support in conducting this study.

I am immensely grateful to **Prof.Dr.R.RAJENDRAN, M.D.,D.A**., Additional Professor of Obstetric Anaesthesia Services, Institute of Obstetrics and gynaecology, Madras medical college & research institute for his valuable guidance and supervision in conducting this study.

I am very grateful to **Dr.Kamalini Sridharan , M.D.,D.A**., Additional Professor of Speciality Services, **Dr.C.R.Kanyakumari, M.D.,D.A**., Additional Professor of Cardiothoracic Anaesthesia, for their constant motivation and valuable suggestions.

I am thankful to **Dr.T.Venkatachalam, M.D.,D.A**., Registrar, Department of Anaesthesiology, for his suggestions in making this work complete.

I am greatly indebted to my guide **Dr.L.Parthasarathy M.D.,D.A.,** for his inspiration, guidance and comments at all stages of this study.

I am thankful to all assistant professors and teachers for their guidance and help.I am thankful to all my colleagues for the help rendered in carrying out this dissertation.

I am thankful to **Dr.Swaminathan.R, M.Sc PhD**., for his help in analysis of data.

Last, but not the least, I thank all my patients for their kind co-operation who made this study feasible.

CONTENTS

INTRODUCTION

Normal pregnancy is characterized by unique physiological changes. It is mandatory for an anesthesiologist to understand these changes and their anesthetic implications.

Pregnancy induced hypertension (PIH) is a disorder of unknown etiology affecting 5-10% of all pregnancies characterized by the development of hypertension with proteinuria after 20 weeks of gestation.

Hypertension-Sustained systolic pressure of at least 140mmHg or a sustained diastolic pressure of at least 90 mmHg that occurs after 20 weeks of gestation in a woman with previously normal blood pressure.

Maternal complications of severe pregnancy induced hypertension include pulmonary edema, intracerebral hemorrhage and renal failure. Fetal complications include intra uterine growth retardation (IUGR), perinatal mortality.

Management of severe pregnancy induced hypertension requires multidisciplinary approach.

Definitive treatment consists of termination of pregnancy along with prevention of seizures and control of blood pressure.

The drugs used in the control of blood pressure are oral antihypertensives like Alphamethyldopa and intravenous agents like Hydralazine, Labetalol, Nitroglycerin etc.

Intravenous Labetalol injection is a unique drug with both alpha and beta adrenergic receptor blocking properties. It has both blood pressure and heart rate reducing properties. This makes it a good choice in treating high blood pressure in severe pregnancy induced hypertension patients. Our study is to find out the efficacy of intravenous Labetalol injection in the acute preoperative control of high blood pressure in severe pregnancy induced hypertension (PIH) patients.

AIM OF STUDY

The aim of this study is to find out and compare the efficacy of intravenous Labetalol injection with the routinely used regimen of oral antihypertensives tablet Alphamethyldopa and tablet Nifedipine in the acute preoperative control of high blood pressure in severe pregnancy induced hypertension patients.

NORMAL PREGNANCY&PREGNANCY INDUCED HYPERTENSION

Normal pregnancy is characterized by unique physiological changes. It is mandatory for an anesthesiologist to understand these changes and their anesthetic implications.

PHYSIOLOGY OF NORMAL PREGNANCY

CARDIOVASCULAR SYSTEM

PARAMETER	CHANGE	AMOUNT
Heart rate	Increase	20 – 30 %
Stroke volume	,,	20 – 50 %
Cardiac output	,,	30 – 50%
Central venous pressure	-	-
Pulmonary capillary wedge pressure	-	-
Systemic vascular resistance	Decrease	20%
Pulmonary vascular resistance	,,	30%
Systemic blood pressure	,,	midtrimester10-15mmHg,then rises

Supine hypotension syndrome

Up to 10% of pregnant patients at term show signs of shock when assuming supine position.

Exacerbated By

- central neuraxial blockade
- vasodilators
- anesthetic agents

Minimised by

- left uterine displacement accomplished by keeping a wedge below right hip or tilting the table.

Electrocardiography

- Right axis deviation
- Right bundle branch block
- ST depression of 1mm on left precordial leads
- T wave inversion L3, V2, 3
- Rotation +/- 15 degrees (QRS axis)

Echocardiography

- Tricuspid regurgitation
- Pulmonary regurgitation
- Mitral regurgitation
- Increased left ventricular end diastolic volume
- Increased left atrial size

Hematological system

- Increase in blood volume by 45%

- Increase in red cell volume by 30%
- So physiological anemia
- All coagulation factors especially 1, 7 increased
- Platelet count decreased in 3rd trimester

Respiratory system

Functional residual capacity	Decreased	20%
Tidal volume	Increased	50%
Respiratory rate	,,	10 – 15 %
Minute ventilation	,,	30 – 40 %
PaCo2		30 mmHg

- Pregnant mothers desaturate faster
- In an emergency setting 4 maximum capacity breaths with 100% O2 should be sufficient
- Edema, capillary engorgement of mucosa of airway is common

Gastrointestinal system

- Progesterone relaxes smooth muscle and impairs esophageal and intestinal motility
- So increased risk of aspiration

Central nervous system

Increased sensitivity to local and general anaesthetics

- Local anesthetic requirement reduced qualitatively and quantitatively

- Minimum alveolar concentration of Halothane decreased by 25%
- Minimum alveolar concentration of Isoflurane decreased by 40%
- Mechanism – progesterone induced sensitivity
- Increased concentration of endogenous opioid ligands

Renal system

- Increased glomerular filtration rate (GFR)

PARAMETER	PREGNANT	NON PREGNANT
Creatinine clearance	140-160 ml/mt	90-110ml/mt
Urea	2 – 4.5mmol/lt	6 – 7 m mol/lt
Creatinine	25-75 micromol/lt	100micromol/lt
PH	7.44	7.4
HCO3	18-22 m mol/lt	23-26 m mol/lt

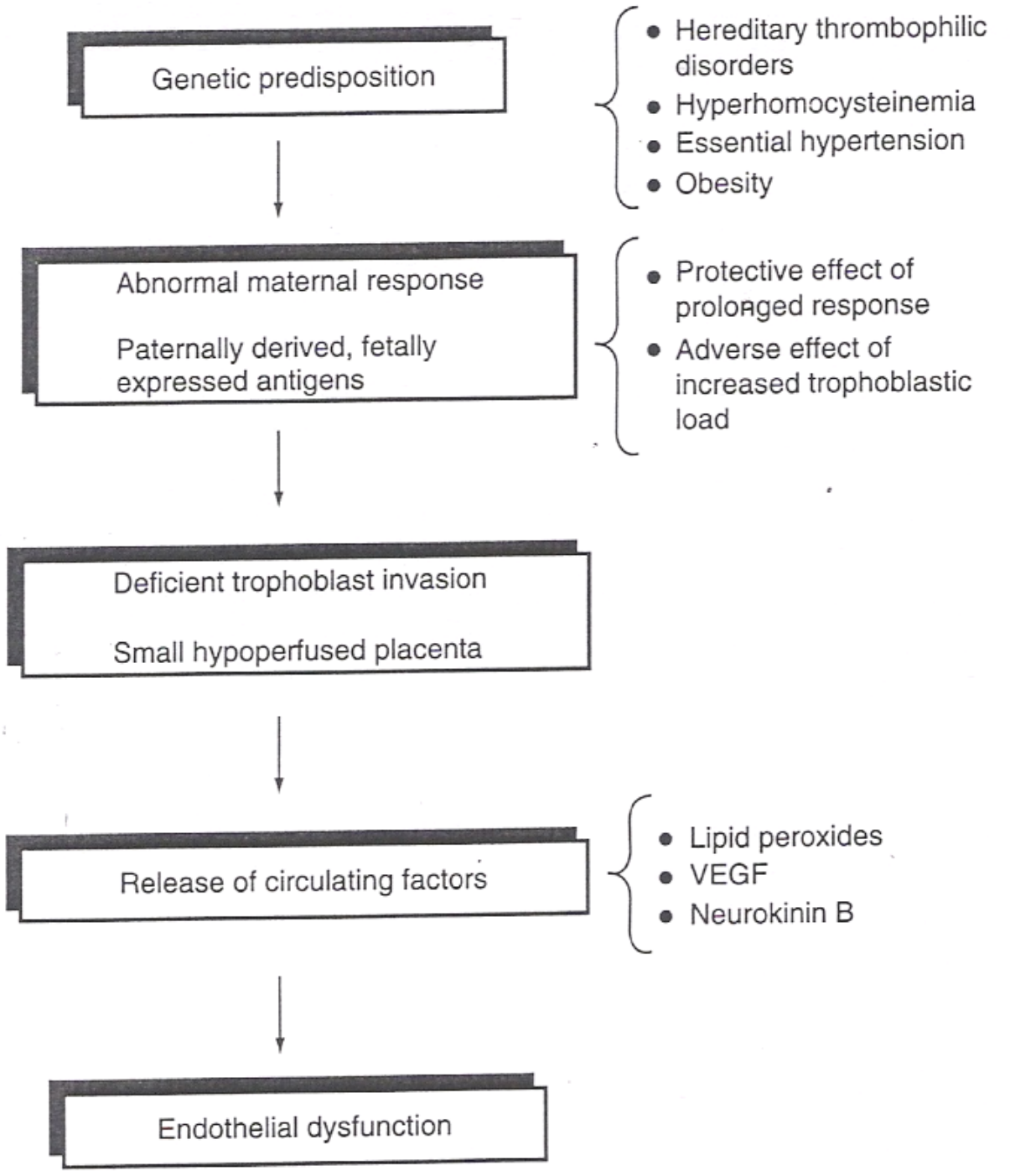
- Glycosuria common due to increased glomerular filtration rate and reduced renal tubular absorption

FETO-PLACENTO-UTERINE CIRCULATION

- Uterine blood flow at term about 500 – 700 ml/mt
- About 80% of uterine blood flows through intervillous space
- 40 – 50 % of fetal cardiac output goes to placenta
- Umbilical capillaries traverse the chorionic villus
- Chorionic villi and intervillous spaces provide the interface for maternal and fetal circulation
- Uterine blood flow lacks autoregulation so

Uterine blood flow = uterine arterial pressure – uterine venous Pressure
Uterine vascular resistance

PROPOSED PATHOGENESIS OF PREGNANCY INDUCED HYPERTENSION



SEVERE PREGNANCY INDUCED HYPERTENSION (PIH)

Pregnancy induced hypertension (PIH) is a disorder of unknown etiology affecting 5-10% of all pregnancies.

Definition- Development of hypertension with proteinuria after 20 weeks of gestation.

Hypertension-Sustained systolic pressure of atleast 140mmHg or a sustained diastolic pressure of at least 90mmHg that occurs after 20 weeks of gestation in a woman with previously normal blood pressure.

Proteinuria->300mgm in 24hour urine collection.

Features of Pregnancy induced hypertension

FACTORS	MILD	SEVERE
Systolic blood pressure	<160mmHg	>160mmHg
Diastolic blood pressure	<110mmHg	>110mmHg
Urinary protein	<5gm/24hr Dipstick+or2+	>5gm/24hr Dipstick3+or4+
Headache	No	Yes
Visual disturbance	No	Yes
Epigastric pain	No	Yes
Right upper quadrant pain	No	Yes

Pulmonary edema	No	Yes
Cyanosis	No	Yes
HELLP	No	Yes
Platelet count	>100000/cumm	<100000/cumm

Risk factors

Primi,teenage pregnancy,history of previous preeclampsia,family history,renal disease,chronic hypertension,obesity,diabetes mellitus,activated protein C resistance(factor V mutation),protein S deficiency,Anti phospholipid antibody syndrome,hyperhomocysteinuria,smoking,stress,hydatiform mole.

PATHOGENESIS

Immunologic features

The fetus acquires 50% of its genes from the father thus it represents a paternal allograft that interacts with maternal tissue as fetal trophoblast migrates into the maternal deciduas after implantation.

True intervillous blood flow is established at 12weeks gestation &in normal gestation a second wave of trophoblastic invasion occurs at 14-16 weeks gestation resulting in disruption of muscular integrity of the maternal spiral arteries, which leads to adrenergic denervation and converts them into low resistance vessels.

At the same time biochemical adaptations occur in maternal vasculature with an increased dominance of endothelium dependant vasodilators prostaglandin PGI2 Nitric oxide (NO).

In women with pregnancy induced hypertension a failure of secondary trophoblastic invasions of the deciduo-myometrial junction occurs. This failure

results in a high resistance, low flow utero placental circulation and consequent placental ischemia and hypoxia. These changes represent an aberrant immunological mechanism. Some women develop pregnancy induced hypertension (PIH), some women develop intra uterine growth retardation (IUGR).

Genetic factors

A molecular variant of angiotensinogen (Angiotensinogen gene T235) angotensinogen II type I Receptor.

FactorV Leiden mutation leading to increase in resistance to activated protein C.

Endothelial factors

Vascular endothelium is a metabolically active interface between blood and underlying tissue. Vascular endothelial damage and dysfunction is the common pathological feature of Pregnancy induced hypertension and occurs in the placental decidual vessels and renal microvasculature.

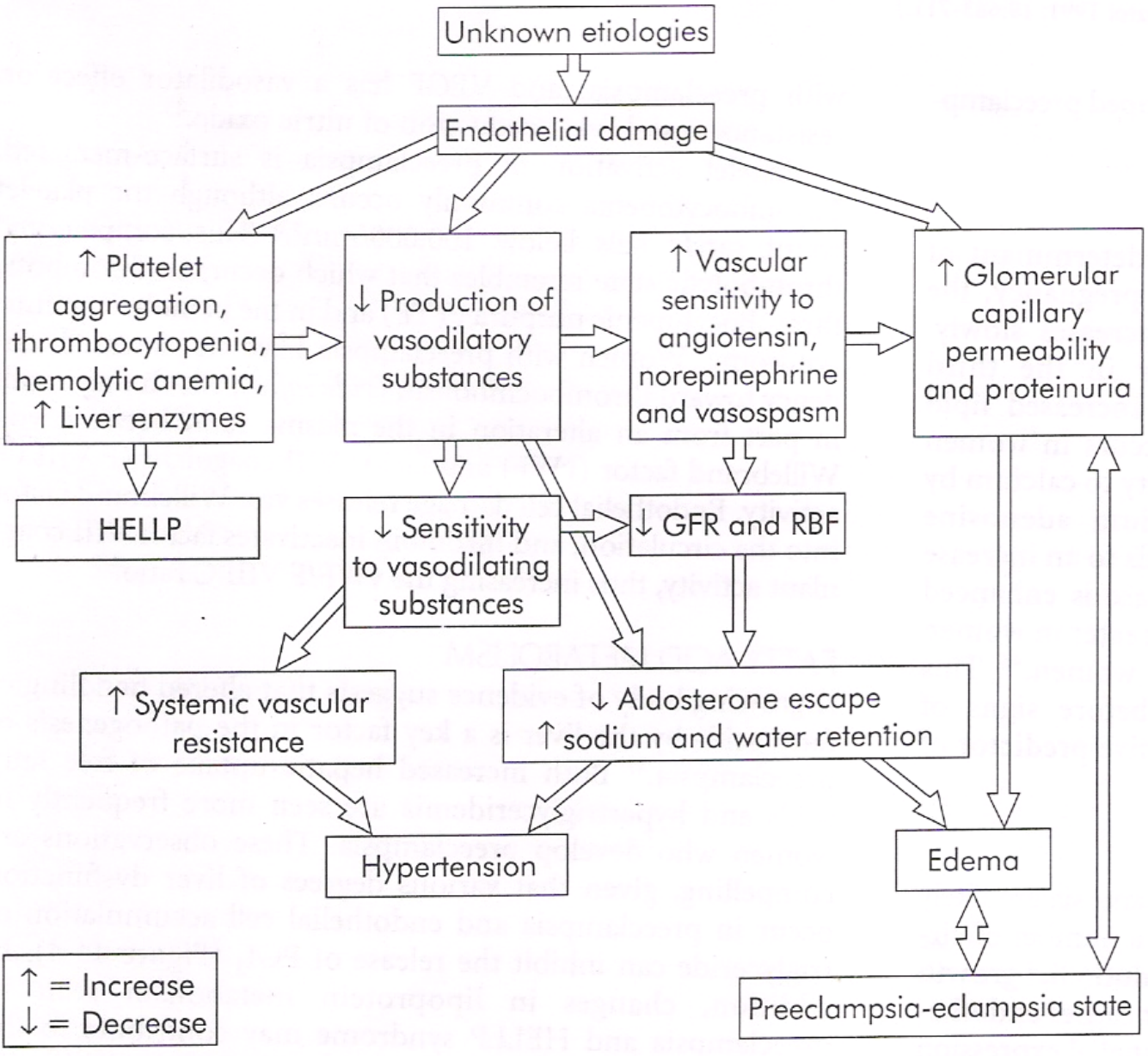
Platelet factors

Platelet activation and aggregation leads to imbalance between vasodilators (Prostacyclin I2&Nitric oxide) and vasoconstrictors (thromboxane A2&5HT)

Coagulation factors

Vascular endothelial growth factor (VEGF)

MECHANSISAM OF ENDOTHELIAL DAMAGE LEADING TO PIH



Pathophysiology

Cardiovascular changes

Blood pressure

Flattening of normal diurnal blood pressure pattern

Labile blood pressure.

Blood volume reduced in some women

Increased level of Atrial natriuretic peptide.

Hemodynamic changes

varied &complex

changes with disease, pregnancy, therapy.

Cardiac function

Normal heart rate

Central venous pressure is misleading

Poor correlation between central venous pressure & pulmonary capillary wedge pressure.

Large bolus of fluid to predetermined central venous pressure can lead to pulmonary edema.

Colloid oncotic pressure

	Pregnancy induced hypertension	Normal
Antepartum	18 mm	22mm
Postpartum	14mm	17mm

Hematological changes

Hypercoagulopathy

Activation of fibrinolytic system

Platelet activation

Renal function

Glomerular filtration rate decreased by 25%

Proteinuria

Hypeuricemia>5.5mg% associated with perinatal morbidity and mortality

Oliguria<400ml/24hours

Endocrine system

Renin angiotensin aldosterone system increased in normal pregnancy while it is suppressed in pregnancy induced hypertension

Respiratory system

Pharyngo laryngeal edema

Pulmonary edema-3%of cases

30%-antenatal

70%-postnatal due increased fluid administration before delivery.

Hepatic function

Increased Alanine transaminase

Epigastric/subcostal pain

Neurolgical changes

Severe headache, visual disturbances, central nervous system hyperexcitability, hyperreflexia, seizures.

Seizures can happen even if blood pressure<140/90(20%cases)

Uteroplacental perfusion

Decreased

HELLP syndrome

Severe form of Pregnancy induced hypertension

1.Hemolysis-Abnormal peripheral smear & serum bilirubin>1.2mgm

2.Platelet count <100,000/l

3.AST>70IU/l&LDH>600U/l

Management of severe PIH

Management of severe pregnancy induced hypertension requires multidisciplinary approach.

Prophylaxis

Aspirin 60 –100mgm/day. Not well established

Oral calcium 2gm/day. Not well established

Definitive treatment consists of termination of pregnancy along with prevention of seizures and control of blood pressure.

Obstetric management

Regardless of gestational age immediate delivery is advocated in

1.Persistant severe hypertension for24-48hrs

2.Progressive thrombocyopenia (<100000)

3.Progressive renal dysfunction (urine output<0.5ml/kg/mt, serum creatinine 1mg%above baseline)

4.Premonitary signs of eclampsia

5.Fetal jeopardy

6.Pulmonary edema

7.Elevated liver enzymes ALT/AST>2times normal with abdominal pain

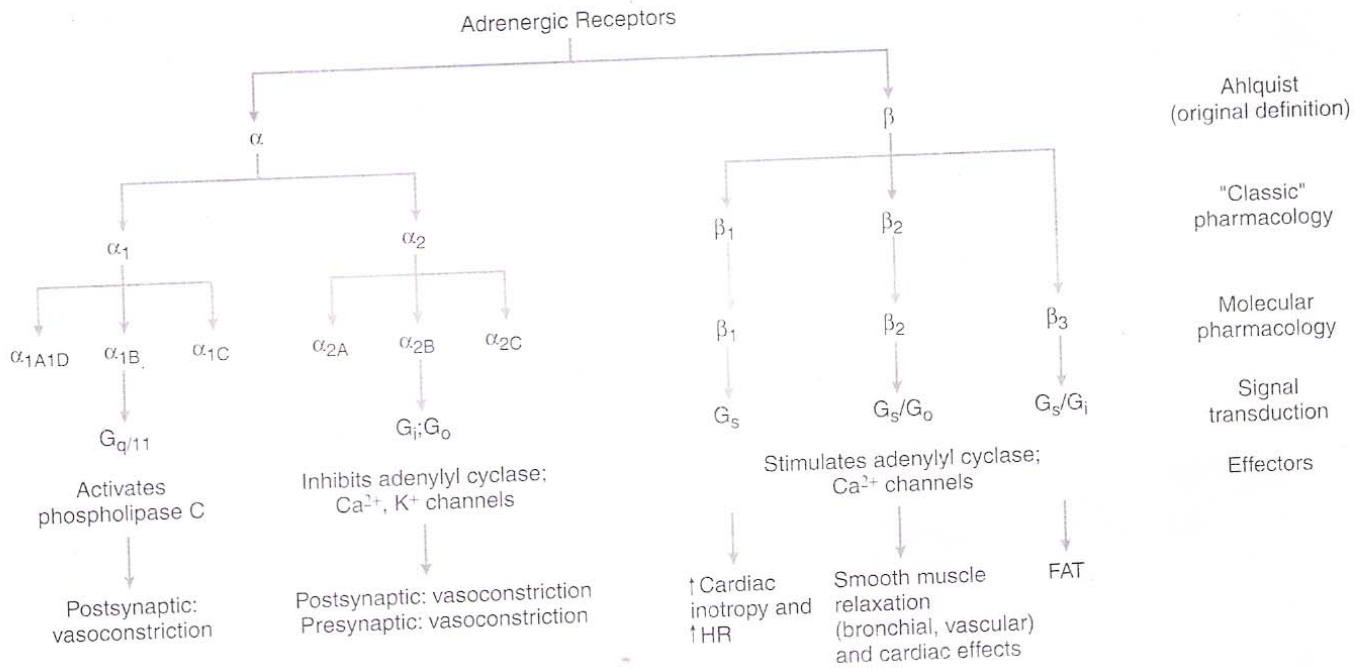
8.A.F index<2

Drug therapy

Magnesium sulphate for seizure prophylaxis.

Antihypertensives-to bring diastolic blood pressure between 105-125 mmHg and Mean arterial blood pressure 90-105 mmHg.

The drugs used in the control of blood pressure are oral antihypertensives Alphamethyldopa, Nifedipine, Labetalol, intravenous agents like Hydralazine, Labetalol, Nitroglycerin etc.


Adrenergic Receptors
α
β
α1
α2
β1
β2
β3
α1A1D
α1B
α1C
α2A
α2B
α2C
β1
β2
β3
Gq/11
Gi;Go
Gs
Gs/Go
Gs/Gi
Activates phospholipase C
Inhibits adenylyl cyclase; Ca2+, K+ channels
Stimulates adenylyl cyclase; Ca2+ channels
Postsynaptic: vasoconstriction
Postsynaptic: vasoconstriction
Presynaptic: vasoconstriction
↑ Cardiac inotropy and ↑ HR
Smooth muscle relaxation (bronchial, vascular) and cardiac effects
FAT
Ahlquist (original definition)
"Classic" pharmacology
Molecular pharmacology
Signal transduction
Effectors

PHARMACOLOGY OF LABETALOL

Antihypertensive agent

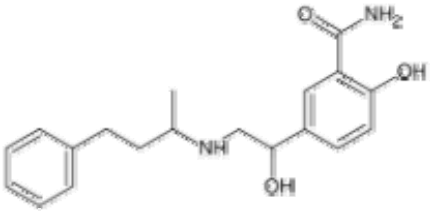
Belongs to class Betablockers

Chemistry

2-hydroxy-5-(1-hydroxy-2-(4-phenylbutan-2-ylamino0-ethyl)-benzamide

Formula C19H24N2O3

Molecular mass 328.406g/mol



Mechanism of action

Competitive antagonist of alpha1, beta1 Adrenergic receptors & agonist of beta2 Adrenergic receptors.

Clinical formulation contains 4 diastereoisomers with net beta to alpha blocking potency3: 1 for oral Labetalol and 7:1 for intravenous Labetalol.

Adrenergic receptors have been divided into alpha and beta receptors and further subdivided into alpha1, alpha2 and beta1, beta2, beta3 receptors.

Alpha1 receptors are present mainly in smooth muscle mediating vasoconstriction.

Alpha2 receptors are present in presynaptic membrane.

Beta1 receptors are present mainly in heart.

Beta2 receptors found in smooth muscle cells mediating relaxation.

After Adrenergic receptor stimulation, the extracellular signal is transformed into an intracellular signal by a process known as signal transduction in which alpha1and beta receptors are coupled to G proteins. G proteins are found on the

inner surface of the cell membrane. G proteins when activated can modulate the synthesis or availability of intracellular second messangers.

Pharmacokinetics

Oral absorption-90%
Bioavailability-20-40%(extensive first pass metabolism in liver)
Protein binding-50%
Metabolism-oxidative biotransformation and glucuronidation in liver
Elimination half-life is 5-8hours

Phamacodynamics

Clinical formulation contains 4 diastereoisomers with net beta to alpha blocking potency3;1 for oral Labetalol and 7:1 for intravenous Labetalol.
Reduces systemic blood pressure
Reduces heart rate
Cardiac output remains unchanged.
Peak blood pressure lowering effect is in 5-10 minutes.

Adverse effects

Orthostatic hypotension
Bronchospasm in susceptible individuals
Congestive heart failure
Heart block
Bradycardia
Fatigue
Drowsiness

Uses

Systemic hypertension

Hypertensive crisis

Pregnancy induced hypertension

Anginapectoris

Contraindications

Congestive heart failure

Heartblock

Hypotension

Peripheral vascular disease

Formulation

Oral tablets-50,100,200,300mgm (max2.4gm/day)

Intravenous injection-5mg/ml(max300/day)

PHARMACOLOGY OF ALPHAMETHYLDOPA

A centrally acting antihypertensive

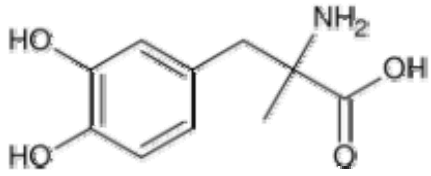
CHEMISTRY

2-amino-3-(3,4-dihydroxyphenyl)-2metyl-propanoicacid

An analogue of 3,4-dihydroxy-L-phenyl alanine (DOPA)

Formula C10H13NO4

Molecular mass 211.215g/mol



Mechanism of action

Alphamethyldopa gets converted into Alphamethyldopamine then to Alpha methylnorepinephrine. Alphamethylnorepineprine replaces Norepinephrine in neurosecretory vesicles in brainstem. It acts as an Alpha2 Adrenergic receptor agonist, attenuates the output of vasoconstrictor Adrenergic signals to peripheral sympathetic nervous system.

Pharmacokinetics

When administered orally it is absorbed by active amino acid transporter with 50% bioavailability.

Peak plasma concentration-2-3hours

Metabolized in liver (50-70 %sulfate conjugates &other metabolites)

Elimination half-life 2 hours

25% of parent drug and Metabolites excreted in urine.

Pharmacodynamics

Fall in systemic vascular resistance without much change in heart rate, cardiac output, and postural hypotension.

Reverses left ventricular hypertrophy in 12 weeks without apparent relationship to degree of change in arterial pressure.

Maximum effect seen 6-8 hours after oral dose.

Duration of action of single dose-24hours (so single/twice daily dose)

Adverse effects

Sedation

Dry mouth

Decrease in libido

Parkinsonian signs

Hyperprolactinemia-galactorrhoea

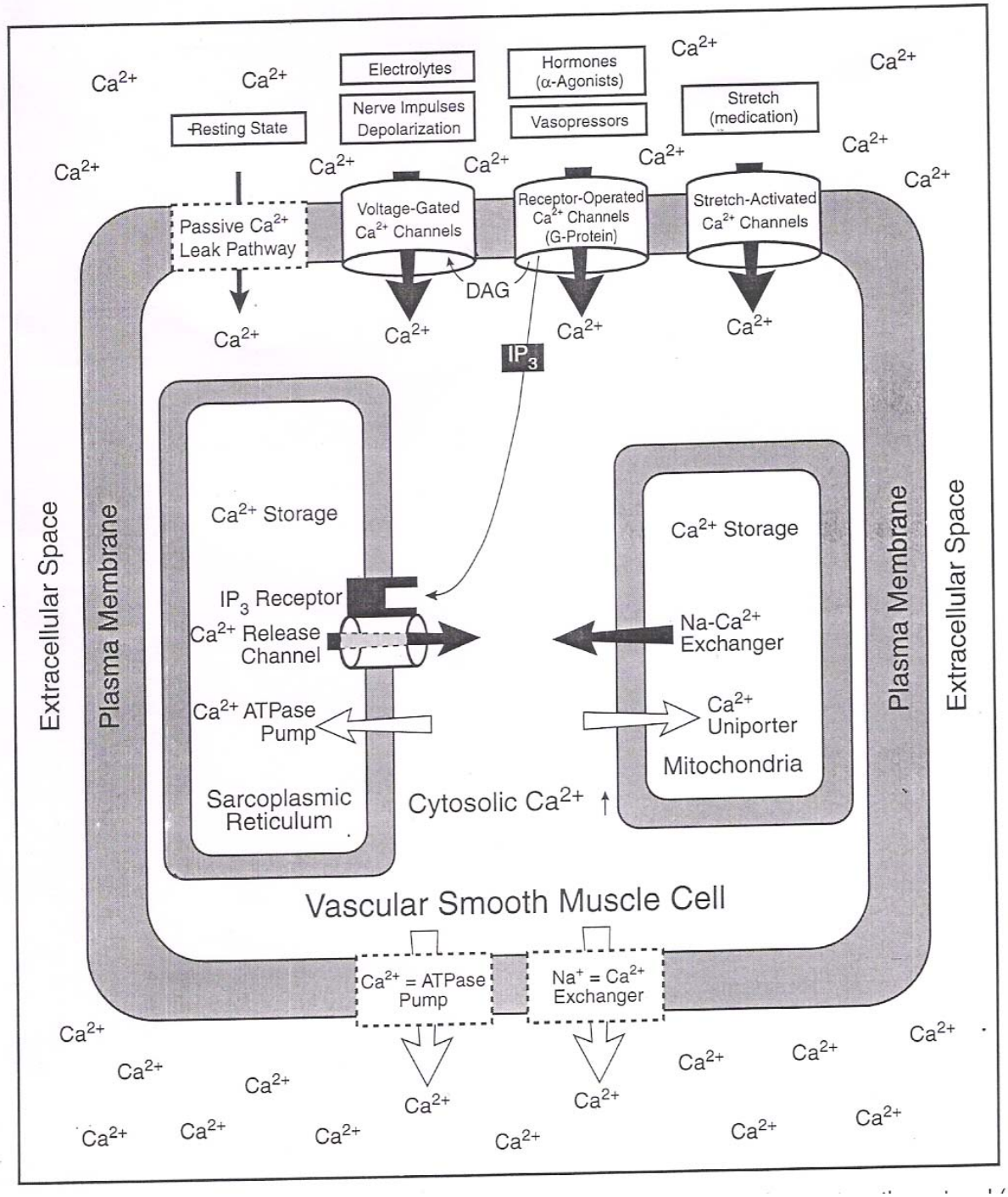
Bradycardia

Elevated liver enzymes

Hepatotoxicity

Hemolytic anemia

CALCIUM ION ENTRY AND EXIT FROM A VASCULAR SMOOTH MUSCLE



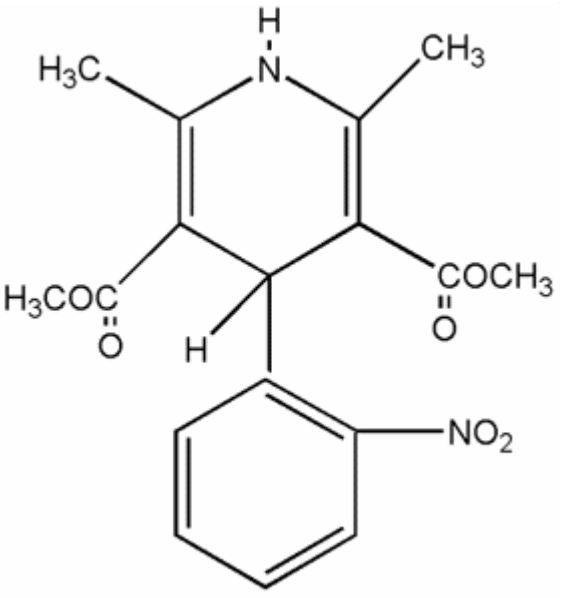
PHARMACOLOGY OF NIFEDIPINE

Chemistry

Antihypertensive belonging to class of Calcium channel blockers

1,4,-dihydropyridine subclass

Dimethyl2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate



C17H18N2O6

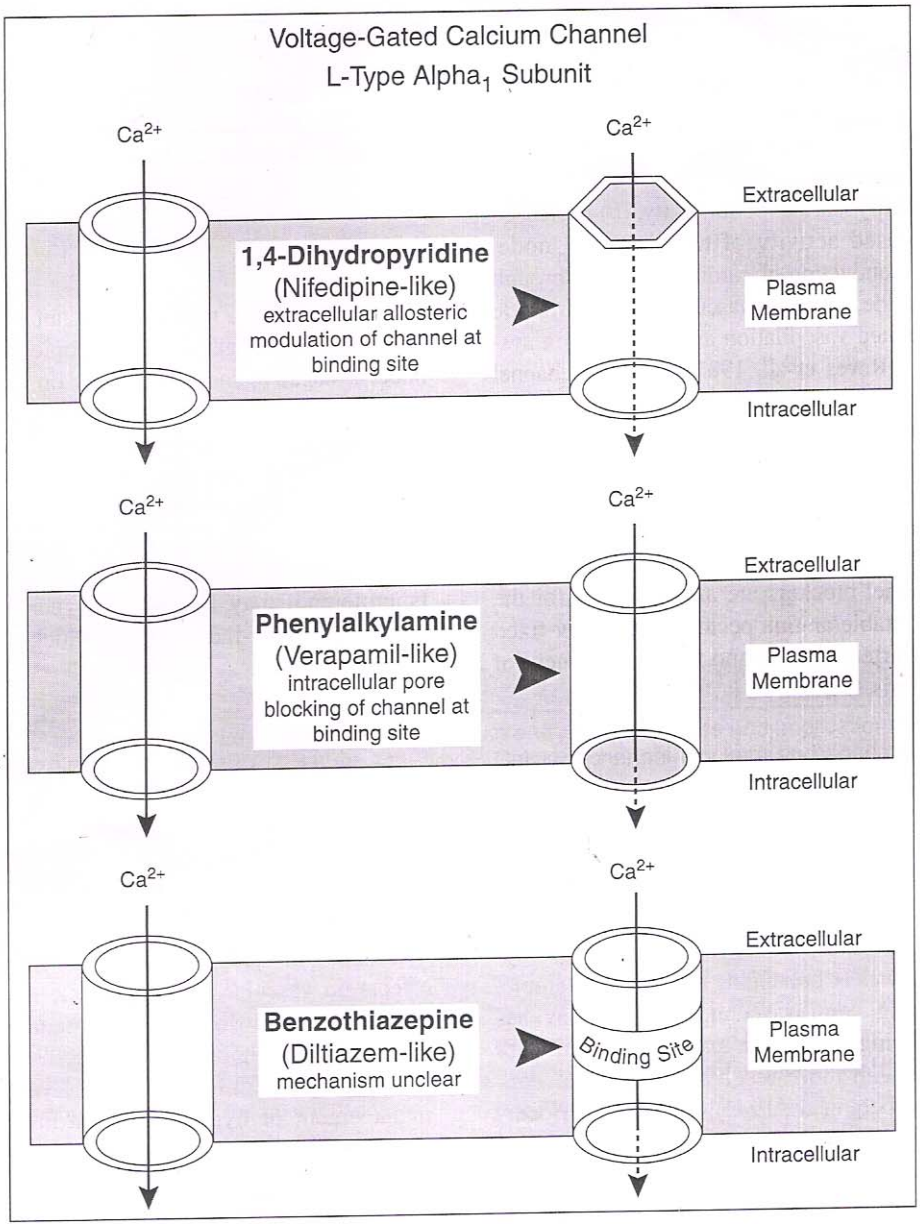
Molecular mass 346.335g/mol

Mechanism of action

Voltage gated Calcium channels are present in cell membrane of all skeletal muscle, vascular smooth muscle, cardiac cell, mesenteric muscle, neurons.

Of the two types (L&T) of voltage gated Calcium ion channels present in the cardiovascular system, L type is the main channel for slow and sustained Calcium ion entry into vascular smooth muscle cells.

MECHANISM OF ACTION OF CALCIUM CHANNEL BLOCKER



L type Calcium channel has 5 subunits-alpha1, alpha2, beta, gamma, delta, theta. Alpha1 subunit forms the central part of Calcium ion channel and provides the main pathway for Calcium ion entry into cell.

Direct activation of vascular smooth muscle cell voltage gated Calcium ion channel by nervous stimulus initiates an action potential, calcium ion influx and myofilament activation (excitation-contraction coupling).the intracellular Calcium combines with Calmodulin, the calcium binding protein to form the Calcium-Calmodulin complex.This complex activates Myosin and causes the formation of cross bridges with Actin. These cross bridges begins the process of muscular contraction.

Pharmacokinetics

Oral absorption-90%
Bioavailability-60%
Protein binding –90%
Metabolism by liver is complete.
Metabolites inactive and excreted by urine
Elimination half life-2-5hours

Pharmacodynamics

Decreases systolic blood pressure, diastolic blood pressure,
Heart rate may increase (reflux tachycardia)
Myocardial depression (mild)
Coronary artery dilation
Peripheral artery dilation.

Adverse effects

Headache, flushing

Excessive myocardial depression in preexisting left ventricular dysfunction/concomitant Betablocker therapy

Therapeutic uses

Hypertension

Angina pectoris

Raynauds phenomenon

Tocolytic

Anal fissures

PHARMACOLOGY OF NITROGLYCERIN

Antihypertensive.

Chemistry:

Chemical name 1,3 - dinitrooxypropan-2-yl-nitrate

Formula $C_3H_5N_30_9$

Molecular weight : 227.1

Pharmacokinetics

Volume of distribution	:	3.3.1 /kg
Plasma protein binding	:	60%
Oral Absorption	:	Incomplete
Presystemic metabolism	:	Extensive
Plasma half life range	:	1-3 min

Lipophilic, which allows rapid and complete absorption from skin and mucosa.

Metabolism:

Rapid liver degradation hydrolysis by nitrate reductase which result in low bioavailability. Thus bioavailability is much higher when drug is given transmucosally by sublingual, translingual (spray), transmucosal (buccal) or transdermal routes or intranasal route.

It is excreted in bile and urine.

Formulations

Tablets	:	0.15 - 0.6mg
Spray	:	0.4mg/metered dose Spray

Surfaced release capsule	:	2.5 - 9mg
Buccal (Transmucosal)	:	1mg
Ointment	:	15 mg/inch
Transdermal disc	:	1 disc (2.5-15mg)
Intravenous	:	1-2. microgm/kg

PHARMACODYNAMICS

Mechanism of action

The nitrates enter the smooth muscle cell and are converted to reactive (NO) or S-nitrosothiol which stimulates guanylate cyclase metabolism to produce cGMP. A cGMP dependent protein kinase is stimulated with resultant protein phosphyorylation in smooth muscle. This leads to a dephosphorylation of the mysoin light chain and smooth muscle relaxation.

CARDIO VASCULAR SYSTEM

Nitroglycerine induced vasodilation occurs throughout the vascular tree with a dose related specificity.Low doses predominantly produce venodilation.

At higher doses nitroglycerine dilates smaller arterioles and resistance vessels, which reduces after load and blood pressure.

Venodilation produces pre-load reduction, leading to a reduction in myocardial oxygen demand due to lessened ventricular wall stress via reduced chamber size and end - diastolic pressure.

Decreases right atrial, pulmonary artery and pulmonary artery wedge pressure.

Renal arteries, cerebral arteries and cutaneous vessels also dilate.

The indirect effects of nitroglycerine consists of reflexes evoked by baroreceptors and harmonal mechanism responding to decrease in arterial pressure.

The primary mechanism of this reflex is sympathetic discharge consistently results in tachycardia and increased cardiac contractility.

SMOOTH MUSCLE ORGANS

Relaxation of smooth muscle of the bronchi, GIT, GUT.

Adverse effects

Vasodilation
Hypotension
Reflex Tachycardia
Throbbing head ache
Drug rash in transdermal patches
Hypoxaemia via worsening ventilation perfusion mismatch through pulmonary vasodilation.
Methemoglobinemia.

THERAPEUTIC USE

Indications

1. Relief of angina
2. Acute myocardial infarction
3. Acute pulmonary edema
4. Hypertension
5. Oesophageal spasm.

Contra indications

1. Low cardiac output secondary to hypovolemia
2. Obstructive cardiomyopathy
3. Raised intracranial pressure
4. Cardiac Tamponade

Relative contra indication

1. Arterial hypoxaemia & corpulmonale
2. Mitral valve prolapse
3. Glaucoma

DRUG INTERACTIONS:

Hypotension occurs with

1. Calcium channel blockers
2. Antihypertensive agents.
3. Phenothiazines
4. Tricyclic antidepressants
5. Alcohol

PHARMACOLOGY OF MAGNESIUM SULPHATE

Anticonvulsant/Antiarrythmic/Tocolytic

Chemistry

Formula- $MgSO_4.7H_2O$

Molecular mass 120.415

Mechanism of action

Blocks neuronal calcium influx through the glutamate channel.

N-methyl-D-aspartate(NMDA)receptors in hippocampal region are blocked.

Pharmacodynamics

Anticonvulsant activity in severe Pregnancy induced hypertensive patients. Reduces systemic vascular resistance and mean arterial pressure and increases cardiac index, though cardiovascular effects last for about 15 minutes despite continued infusion.

Dose dependant inhibition of uterine muscular contractility(a minimum serum magnesium level of 8 to 10 meq/l is required).Magnesium sulphate did not significantly alter oxytocin stimulation of labour.

Neonatal depression can occur in severe hypermagnesemia.

Orally administered magnesium sulphate has laxative effect.

Broncho dilator.

Pharmacokinetics

Administered intra muscularly /intravenously.

Excreted by the kidneys.

Adverse effects

Dose dependant

Normal serum level	1.5-2.0meq/l
Therapeautic level	4.0-8.0meq/l
Prolonged PQ interval, QRS widening	5.0-10 meq/l
Deep tendon reflex absent	10 meq/l
Sinoatrial/atrioventricular block, Respiratory paralysis	15meq/l
Cardiac arrest	25 meq/l

Adverse effects are monitored by respiration, deep tendon reflexes, urinary output and serum magnesium levels. Inj Calcium gluconate 10 ml slow iv is used to treat magnesium toxicity.

Therapeutic uses

Anticonvulsant

Bronchodilator

Antiarrythmic (torsades des pointes)

Tocolysis

Hypomagnesemia

REVIEW OF LITERATURE

Ramanathan J et al in their study of anesthetic modification of hemodynamic and neuroendocrine stress response to caesarean delivery in women severe preeclampsia observed that after pretreatment with Labetolol or Nitroglycerine mean arterial pressure decreased from 131.5 +/- 4.9 mmHg to 112.2+/- 3.5 mmHg (21).

Vigil – De gracia p et al in their randomized clinical trial (severe hypertension in pregnancy: Hydralazine or Labetalol) observed that Labetalol fulfilled the criteria required for an antihypertensive to treat severe hypertension in pregnancy (26).

Belfort MA et al in their study observed that Labetolol is an ideal agent for blood pressure control in severely hypertensive pregnant women (2).

Gilson GJ et al in their investigation concluded that incidence of pulmonary edema in patients with severe preeclampsia who are treated with Labetalol appears to be a result of an increase in third space fluid accumulation as a manifestation of the severity of their disease, not a direct effect of the drug on cardiac performance (11).

Schobel HP et al in their data indicated that the increases in peripheral vascular resistance and blood pressure that characterize this disorder are mediated, at least in part, by a substantial increase in sympathetic vasoconstrictor activity. (25)

Wallace DH et al in their study concluded that general as well as regional anesthetic methods are equally acceptable for cesarean delivery in pregnancies complicated by severe preeclampsia if steps are taken to ensure a careful approach to either method.(27)

Kwawukume EY et al in their study concluded that Nifedipine and Hydralazine could both be used effectively to control blood pressure in severe preeclampsia. While Hydralazine is administered intravenously and needs strict monitoring, Nifedipine is more effective, is easy to administer orally, less demanding on hospital staff, convenient and more predictable. (14)

El-Qarmalawi AM, et al in their study concluded that Labetalol is better tolerated than Alphamethyldopa, gives more efficient control of blood pressure and may have a ripening effect on the uterine cervix. (8).

Mahmoud TZ, et al in their study observed that Labetalol allows safe prolongation of pregnancies complicated by Pregnancy induced hypertension (PIH). (17)

Kumar N et al in their study observed that there was a decrease in mean arterial blood pressure (MAP) after pretreatment with Nifedipine. The increase in mean arterial pressure (MAP) during laryngoscopy and intubation was higher in the control group compared with Nifedipine pretreatment group. During laryngoscopy and intubation, Mean arterial pressure decreased by 3 mmHg in the Nifedipine pretreatment group, while there was an increase of 14 mmHg in the control group. Heart rate increased in both the groups during the laryngoscopy and tracheal intubation but the increase was higher in the Nifedipine group than in the

control group. Neonatal Apgar scores in both the groups were comparable. These results suggest that sublingual Nifedipine is effective in attenuating the hypertensive response to laryngoscopy and intubation but not the tachycardiac response in parturients with pregnancy induced hypertension (PIH). (13)

Olsen KS et al in their study observed hemodynamic collapse following Labetalol administration in preeclampsia. On the 3rd day after a cesarean section, because of pre-eclampsia, blood pressure was still high, oral Labetalol 100 mg with an 8-hour interval was given, followed by 50 mg i.v. administered over 10 min, twice with a 5-hour interval. The last injection was immediately followed by an atrio-ventricular tachycardia with massive decrease in blood pressure. (20)

Olsen KS et al in their study observed fetal death following Labetalol administration in pre-eclampsia.

Labetalol (Trandate) 50 mg i.v was administered to a pre-eclamptic primigravida with an asphytic fetus prior to cesarean section, in order to reduce the risk of excessive increase in blood pressure during induction of anesthesia. Blood pressure fell rapidly from 170/110 to 115/85 mmHg. A dead infant was born. Oral Labetalol is arguably a suitable remedy for pre-eclampsia, but if i.v administration is necessary, an initial dose of 5-10 mg is recommended. (19)

Chung KS et al in their study concluded that an intermediate dose of Labetalol blunted the heart rate response to laryngoscopy and intubation during rapid-sequence induction in healthy patients but had a minimal effect on blood pressure. (5)

Montan, Sven; et al in their study on effects of Alphamethyldopa on uteroplacental and fetal hemodynamics in pregnancy-induced hypertension observed that Alphamethyldopa in the last trimester in women with pregnancy-induced hypertension reduced maternal blood pressure and heart rate but had no adverse effects on uteroplacental and fetal hemodynamics. (18)

Lee SC et al in their study on effects of Labetalol and Nitroglycerin during induction of anesthesia and endotracheal intubation in hypertensive patients concluded that both drugs blunted the hypertensive response to endotracheal intubation, intravenous Labetalol seemed safer and more effective than Nitroglycerin to attenuate the hypertensive response to laryngoscopy and intubation in hypertensive patients. (15)

Leslie JB, et al in their study on attenuation of the hemodynamic responses to endotracheal intubation with preinduction intravenous Labetalol showed that IV Labetalol at doses up to 0.75 mg/kg offers an effective pharmacologic means of attenuating preoperative hemodynamic responses to endotracheal intubation. (16).

Connell H,et al in their study on general anaesthesia in mothers with severe pre-eclampsia/eclampsia observed that the average increase in systolic arterial pressure was 56.4 mm Hg following laryngoscopy and tracheal intubation. (6)

Scardo,james.A et al in their randomized, double-blind, hemodynamic evaluation of Nifedipine and Labetalol in preeclamptic hypertensive emergencies concluded that Nifedipine increases cardiac index, whereas Labetalol may not do so. (27)

MATERIALS AND METHODS

After obtaining the necessary institutional and ethical committee clearance following study was conducted in the Institute of obstetrics and gynecology, (IOG), Madras Medical college &Research Institute, Chennai .All antenatal mothers were screened for severe pregnancy induced hypertension (PIH) in the casualty department and 40 patients with severe PIH were selected. Informed consent was obtained from them and randomly divided into 2 groups namely group A and group L of 20 each.

Inclusion criteria:(any one of the following)

1. Systolic blood pressure> 160mmHg
2. Diastolic blood pressure>110mmHg
3. Proteinuria (dipsticks)>+3or+4
4. History of oliguria or urine output < 500ml in 24 hours
5. Presenting with imminent features– blurring of vision, epigastric pain, hyperreflexia, HELLP

Exclusion criteria:

1. Secondary hypertension
2. Cardiac arrhythmia
3. Bronchial asthma
4. Diabetes mellitus
5. Complications due to severe Pregnancy induced hypertension like intracerebral hemorrhage, acute left ventricular failure, coagulopathy, bleeding disorders
6. Patients already on oral antihypertensives are not included in-group L.

Selected patients were examined and the nature of disease and its treatment explained to them. They were made to lie down in supine position with a 15 – 25 degree lateral tilt by placing a wedge below the right hip to avoid supine hypotension syndrome/aortocaval compression. All patients were maintained on nil per status since admission. Baseline parameters like weight, height, blood pressure, heart rate, respiratory rate, temperature, spo2, Jugular venous pulse, and fetal heart rate were recorded. A 16G intravenous line was started in the dorsum of left hand and ringer lactate was administered at 85 ml per hour. Urinary bladder was catheterized and urine output monitored. Blood sample was collected and sent for following investigations: Blood grouping/typing, Hb, PCV, urea, creatinine, electrolytes, sugar, uric acid, fibrinogen, platelet count, bleeding time, clotting time.

Group A patients were administered two tablets of Alphamethyldopa 250 mgms and one tablet of Nifedipine 10mgm each with a sip of water in the casualty itself. They were shifted to intensive care unit (ICU) where they were monitored for control of Blood Pressure/progress of pregnancy/seizures. If 3 hours after starting oral antihypertensive combination either the mean arterial pressure (MAP) / diastolic blood pressure (DBP) is found to be more than 125 mmHg/ 105 mmHg then injection Nitroglycerin infusion is administered at 5 microgram/kg/min as a rescue drug.

Group L patients were not administered anything in casualty department. They were shifted to intensive care unit (ICU) where they were monitored for control of Blood pressure/progress of pregnancy/seizures. In the ICU injection Labetalol 20 mgms intravenous was administered slowly and repeated every 10 minutes if necessary.

The aim in both groups of patients is to achieve a target blood pressure of mean arterial pressure 105 – 125 mmHg and diastolic blood pressure 90 – 105 mmHg.

Both group of patients were administered 4 gms of magnesium sulphate intravenously over 30 minutes in 100 ml of Normal saline followed by administration of 1 gm/hr magnesium sulphate I.V. for the next 24 hrs. The patients were monitored for evidence of magnesium toxicity like absence of tendon reflexes, diminished respiration and urine output. If it is found the administration of magnesium sulphate is stopped and calcium gluconate 1 gm I.V. is administered slowly with ECG monitoring.

The following parameters were recorded every 5 minutes during the study.

1. Systolic blood pressure (SBP)
2. Diastolic blood pressure (DBP)
3. Mean arterial pressure (MAP)
4. Heart rate
5. Fetal heart rate
6. Spo2 – room air
7. Urine output (Hourly)

The administration of either Nitroglycerin or Labetalol is tapered / stopped respectively if

1. Diastolic blood pressure < or = 105 mmHg and mean arterial pressure < or = 125 mmHg
2. Heart rate < 60/min
3. Labetalol > 2mgm/kg body weight

4. Fetal heart rate < 120/min or > 160/min

If any patient developed diastolic blood pressure < 90 mmHg or mean arterial pressure < 105 mmHg even after stopping all antihypertensives, patient is administered humidified 100% oxygen by face mask, adequately ventilated and fluid infused rapidly until diastolic blood pressure more than 90 mmHg / mean arterial pressure > 105 mmHg with caution to avoid pulmonary edema.

If any patient developed heart rate < 60 /min and features of symptomatic bradycardia (shortness of breath, light headedness, angina, ischemic changes, cool peripheries, diastolic blood pressure / mean arterial pressure < 90 / 105 mmHg), injection Labetalol is stopped, patient is administered humidified 100%oxygen by face mask, adequately ventilated and fluid infused rapidly until diastolic blood pressure more than 90 mmHg / mean arterial pressure > 105 mmHg, injection atropine 0.3 – 0.5 bolus repeated if necessary at 5 min intervals (maximum 3 mgm) with caution to avoid pulmonary edema.

In our study pregnancy was terminated for obstetric reasons in all patients of both groups. After premedication with 0.2 mgm Glycopyrrolate intramuscular, 10 mgm injection Metaclopromide intramuscular and injection Ranitidine 50 mgm intravenous emergency termination of pregnancy is accomplished by

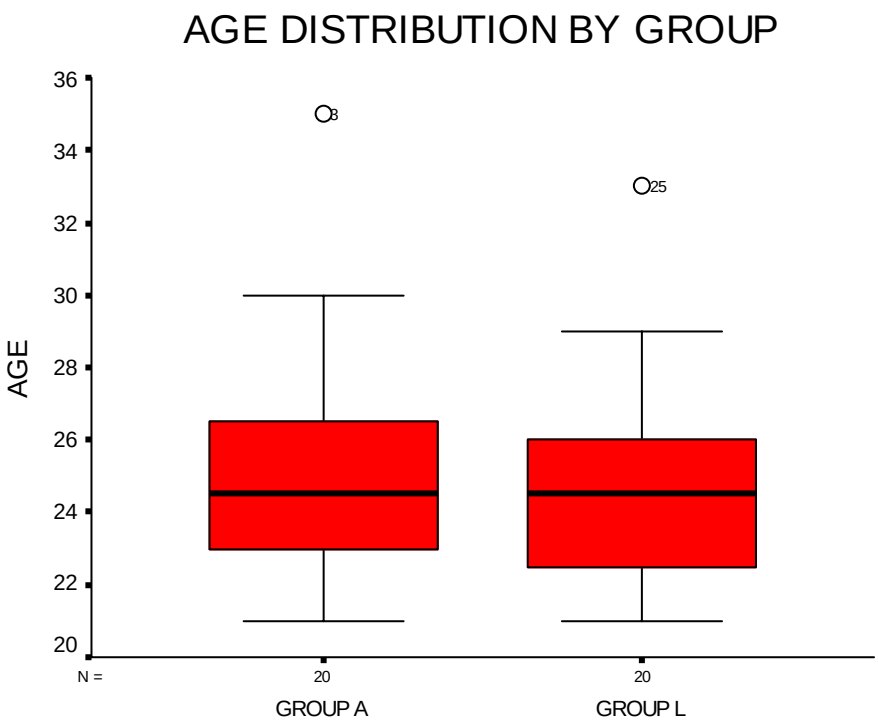
1. Induction of labour and normal vaginal delivery (only one patient in group L who failed to achieve target blood pressure)
2. Emergency LSCS under general anesthesia (4 patients in group A who failed to achieve target blood pressure)
3. Emergency lower segment cesarean section (LSCS) under regional anesthesia (all patient in both groups who achieved target blood pressure)

Patients were explained and informed consent was obtained for LSCS. In the operation theatre anesthesia machine was checked, emergency medicines, suction apparatus, laryngoscopes, appropriate sized endotracheal tubes (ETT), laryngeal mask airway, Guedal's airways were kept ready. Patients were connected to monitors including Non invasive blood pressure, Spo2, ECG, respiration, temperature. All patients were made to lie down in supine position with a 15 – 25 degree lateral tilt by placing a wedge below the right hip to avoid supine hypotension syndrome/aortocaval compression.

Subarachnoid block was chosen as the regional technique. With aseptic precautions patients were administered 2.2 ml of 0.5% Bupivacaine hydrochloride heavy (spinal preparation) in the L3/4 space in the lateral position. All patients were made to lie down in supine position with a 15 – 25 degree lateral tilt by placing a wedge below the right hip to avoid supine hypotension syndrome/aortocaval compression. After ascertaining sensory level of T6 emergency LSCS was allowed to proceed. Any episode of hypotension was managed with administration of humidified 100% oxygen, adequate ventilation, rapid crystalloid infusion, injection ephedrine 6 mg intravenous boluses and injection atropine 0.3 to 0.5 mg boluses if necessary. After the delivery of baby and cord is clamped injection Oxytocin is administered at 20 to 40 IU / hr. Neonatal outcomes were recorded.

For emergency LSCS under general anesthesia patients were made to lie down in supine position with a 15 – 25 degree lateral tilt by placing a wedge below the right hip to avoid supine hypotension syndrome/aortocaval compression. Patients are draped, preoxygenated with 100% o2 for 5 min. Then injection Thiopentone

sodium 5 mg/kg, 2.5% solution was administered over 5 – 15 seconds immediately followed by injection Suxamethonium hydrochloride 1.5 mg/kg body weight rapid push. 20 seconds later cricoid pressure was applied. 45 seconds after the administration of Suxamethonium hydrochloride laryngoscopy is done, patient is intubated with 6.0/6.5/7.0 endotracheal tube. After confirming position of ETT by physical methods ETT cuff is inflated and cricoid pressure released. ETT is secured with tapes, patient is ventilated with N2O/O2 5:5 until baby delivery (4:2 after baby delivery). LSCS is allowed to proceed, injection Oxytocin 20 to 40 IU/hr and injection Fentanyl citrate 100 micrograms intravenous are administered after baby delivery and cord is clamped . Nondepolarising muscle relaxants injection Vecuronium bromide is used if necessary. After the surgery is over the patient is administered injection Neostigmine methylsulphate 50 microgram/kg and Glycopyrrolate 10 microgram/kg to antagonise any residual neuromuscular blockade. After complete recovery of the patient extubation is done. The patient is shifted back to ICU for postoperative care. Neonatal outcomes were recorded.


AGE DISTRIBUTION BY GROUP
AGE
36
34
32
30
28
26
24
22
20
8
25
N =
20
20
GROUP A
GROUP L

RESULTS AND OBSERVATION

The results were evaluated using students t test comparing between the groups and within the group.

TABLE NO-I AGE DISTRIBUTION (YEARS)

	GROUP A(n=20)	GROUP L(n=20)	p value
MEAN	25.2	25	0.84(not significant)
S.D	3.33	2.87	
MEDIAN	24.5	24.5	
RANGE	21-35	21-37	

Table no-1 shows the age distribution range and mean ages observed in both groups.In Group A the mean age is 25.2 years .In Group L the mean age is 25 years. Both Groups are comparable with p value (0.84) not significant.

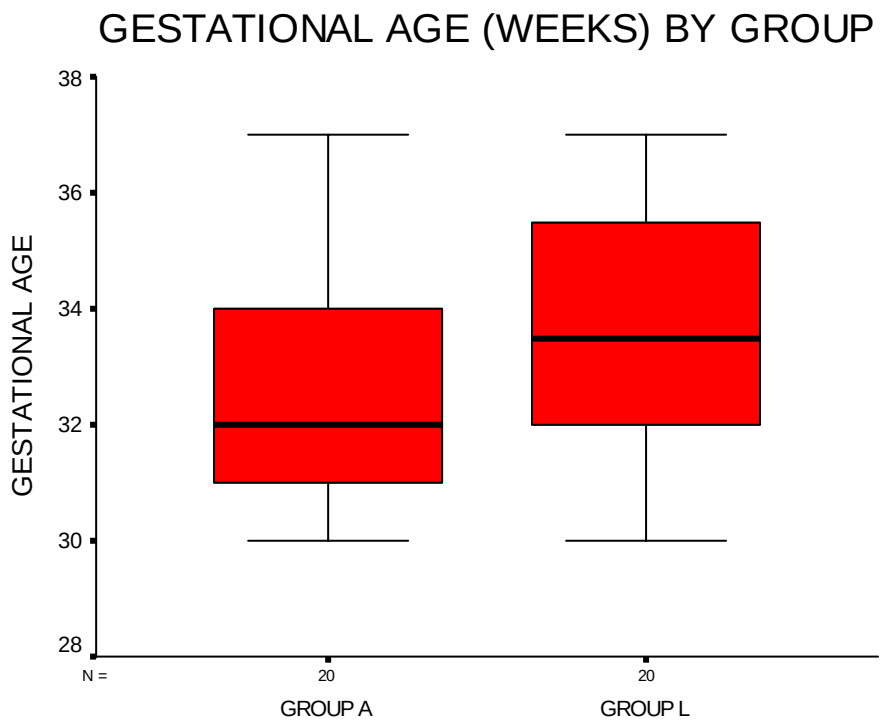


TABLE NO-II GESTATATIONAL AGE (WEEKS)

	GROUPA (n=20)	GROUPL (n=20)	p value
MEAN	32.8	33.5	0.28(not significant)
S.D	1.92	2.11	
MEDIAN	32	33.5	
RANGE	30-37	30-37	

Table no-2 shows the distribution range and mean gestational ages observed in both groups. In Group A the mean gestational age is 32.8 weeks. In Group L the mean gestational age is 33.5 weeks. Both Groups are comparable with p value (0.28) not significant.

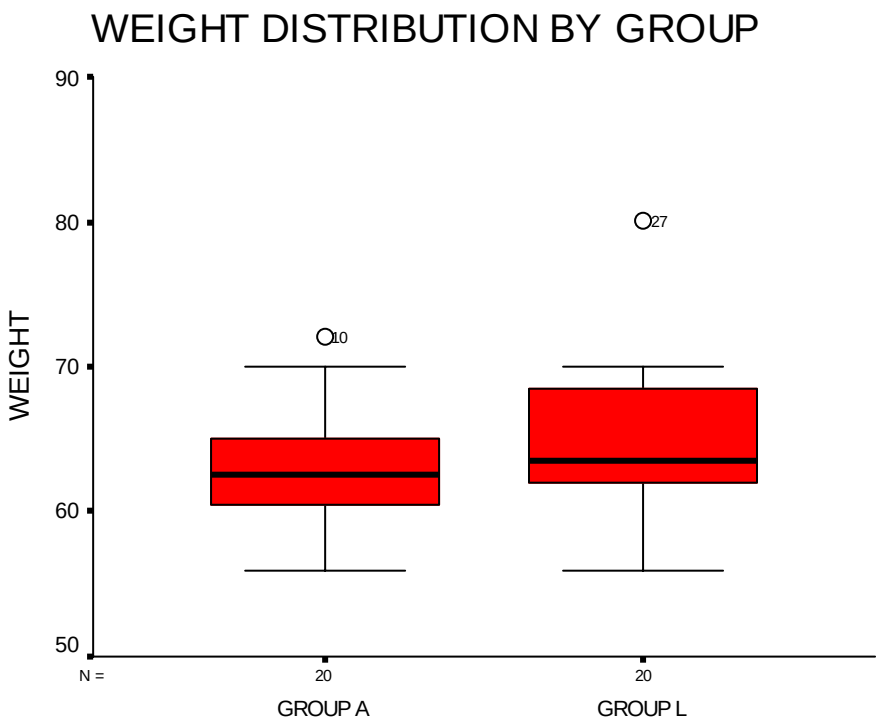


TABLE NO-III WEIGHT DISTRIBUTION (IN KGS)

	GROUPA (n=20)	GROUP L (n=20)	p value
MEAN	63.1	64.8	0.25(not significant)
S.D	3.91	5.44	
MEDIAN	62.5	63.5	
RANGE	56-72	56-80	

Table no-3 shows the distribution, range and mean weight observed in both groups. In Group A the mean weight is 63.1 kgs. In Group L the mean weight is 64.8 kgs. Both Groups are comparable with p value (0.25) not significant.

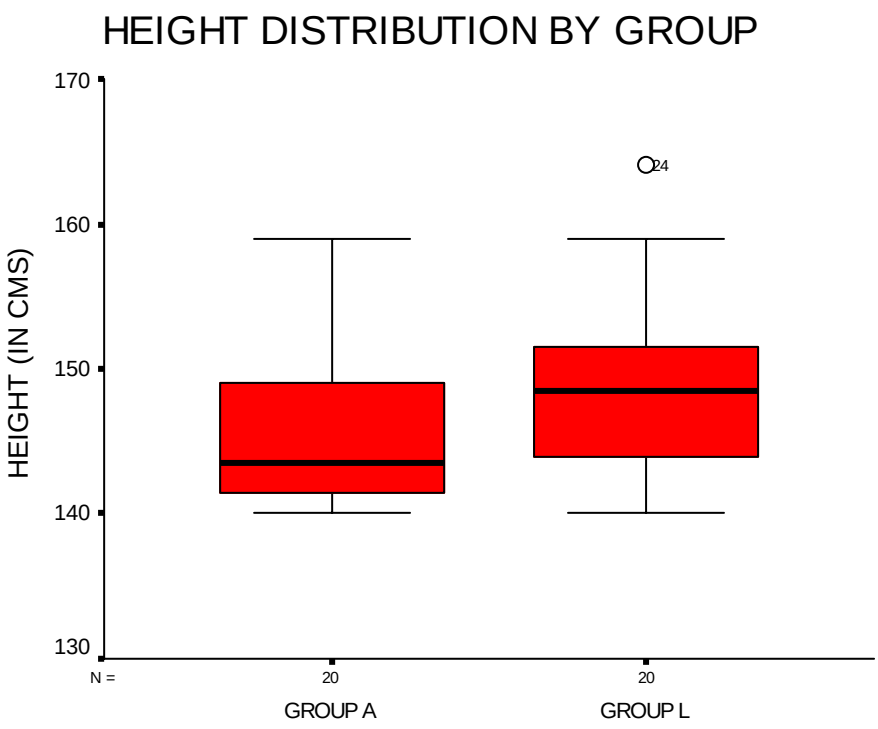

HEIGHT DISTRIBUTION BY GROUP
HEIGHT (IN CMS)
170
160
150
140
130
24
N =
20
20
GROUP A
GROUP L

TABLE NO-IV HEIGHT DISTRIBUTION (IN CENTIMETERS)

	GROUPA (n=20)	GROUPL (n=20)	p value
MEAN	145.8	149.4	0.07(not significant)
S.D	5.77	6.55	
MEDIAN	143.5	148.5	
RANGE	140-159	140-164	

Table no-4 shows the distribution, range and mean height observed in both groups In Group A the mean height is 145.8cms. In Group L the mean height is 149.4cms. Both Groups are comparable with p value (0.07) not significant.

TABLE NO V-DEMOGRAPHIC PROFILE

MEAN VALUES	GROUP A (n=20)	GROUP L (n=20)
AGE (years)	25.2	25
WEIGHT (kgms)	63.1	64.8
HEIGHT (cms)	143.5	148.5

Table no 5 shows the patient characteristics, age height and weight observed in both groups.

TABLE NO-VI FAILURE RATE TO ACHIEVE BLOOD PRESSURE CONTROL

	GROUPA(n=20)	GROUPL (n=20)	p value
FAILURE	20%	5%	0.34(not significant)

Table no-6 shows the failure rate to achieve blood pressure control in both groups. In Group A out of 20 patients 4 patients (20%) failed to achieve blood pressure control despite using injection nitroglycerin as rescue drug. In Group L patients only one patient (5%) failed to achieve blood pressure control .The failure rate between the 2 groups is not statistically significant with p value (0.34)

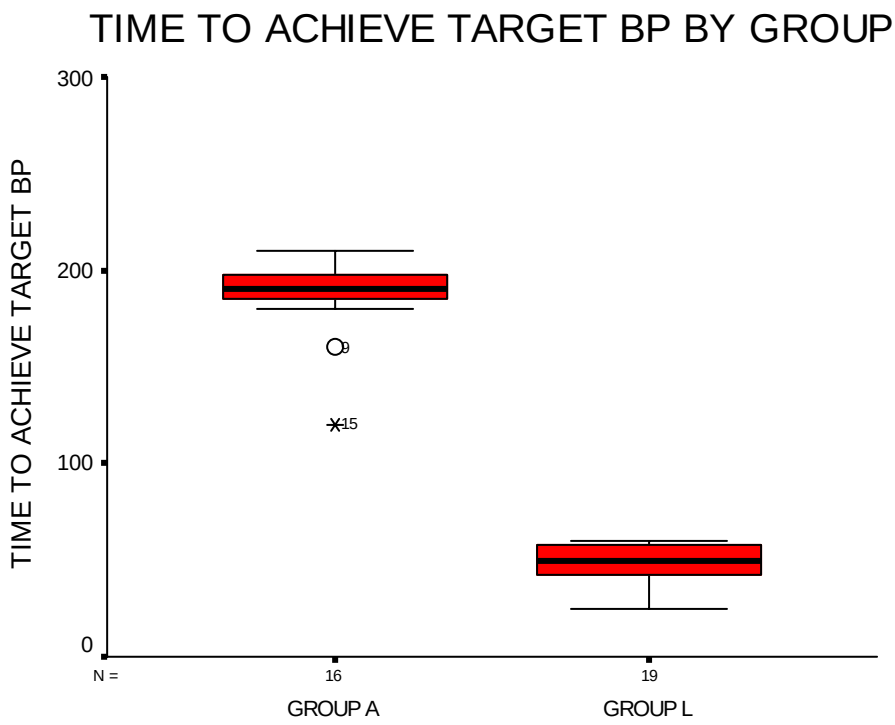


TABLE NO –VII TIME TO ACHIEVE TARGET BLOOD PRESSURE (in minutes)

TIME	GROUPA(n=16)	GROUPL (n=19)	p value
MEAN	185.9	46.8	
S.D	20.75	11.57	<0.001(significant)

Table no-7 shows the mean, standard deviation of the time taken to achieve target blood pressure in both groups. In Group A patients (n=16) the mean time taken to achieve target blood pressure is 185.9 minutes. In Group L patients (n=19) the mean time taken to achieve target blood pressure is 46.8 minutes .The time difference to achieve target blood pressure between the 2 groups is statistically significant (p value<0.001)

MEAN DISTRIBUTION OF SYSTOLIC BP VALUES BY GROUP

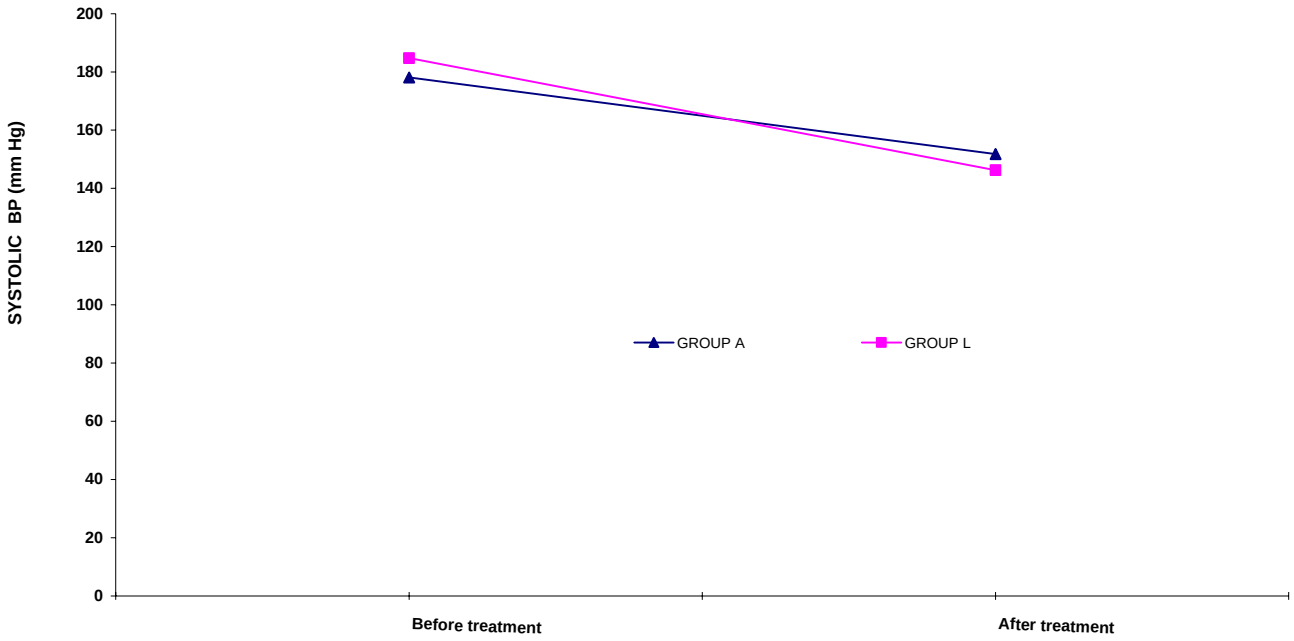


TABLE NO-8 CHANGES –SYSTOLIC BLOOD PRESSURE (mm Hg)

	GROUP A(n=20)	GROUP L(n=20)	p value
BEFORE TREATMENT			
MEAN	178.1	184.7	0.22(not significant)
S.D	14.34	19.16	
	GROUPA(n=16)	GROUPL(n=19)	P value
AFTER TREATMENT			
MEAN	151.8	146.2	0.002(significant)
S.D	5.34	4.50	

Table-no –8 shows the changes in systolic blood pressure in the 2 groups.

In Group A the mean systolic blood pressure before treatment is 178.1 mmHg.

In Group L the mean systolic blood pressure before treatment is 184.7 mmHg.

Both groups are comparable with p value (0.22) not significant.

In Group A the mean systolic blood pressure after treatment is 151.8 mmHg.

In Group L the mean systolic blood pressure after treatment is 146.2 mmHg.

The p value 0.002 suggests the statistical significance that in Group L patients (n=19) achieved better and lower mean systolic blood pressure after treatment than Group A patients (n=16).

MEAN DISTRIBUTION OF DIASTOLIC BP VALUES BY GROUP

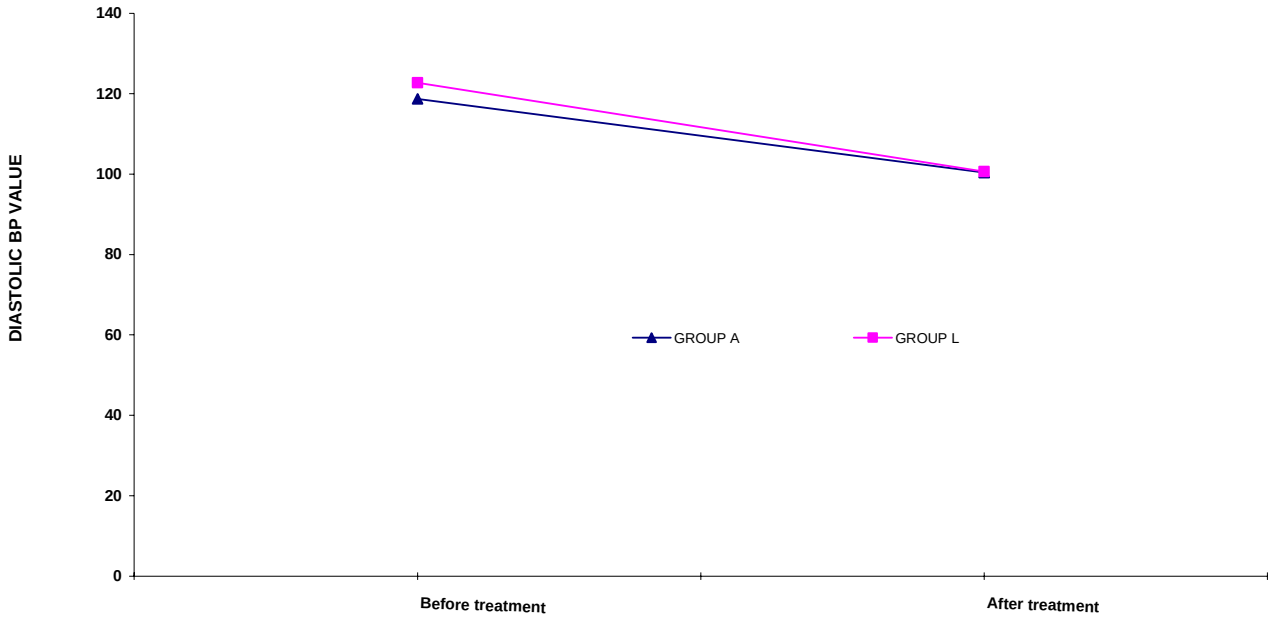


TABLE NO-9 CHANGES-DIASTOLIC BLOOD PRESSURE (mm Hg)

	GROUPA(n=20)	GROUPL(n=20)	p value
BEFORE TREATMENT			
MEAN	118.7	122.7	0.234(not significant)
S.D	12.16	8.43	
	GROUPA(n=16)	GROUPL(n=19)	P value
AFTER TREATMENT			
MEAN	100.4	100.6	0.91(not significant)
S.D	4.15	3.42	

Table no-9 shows the changes in diastolic blood pressure in the 2 groups.

In Group A the mean diastolic blood pressure before treatment is 118.7 mmHg.

In Group L the mean diastolic blood pressure before treatment is 122.7 mmHg.

Both groups are comparable with p value (0.234) not significant.

In Group A the mean diastolic blood pressure after treatment is 100.4 mmHg.

In Group L the mean diastolic blood pressure after treatment is 100.6 mmHg.

There is no statistical significance between the 2 Groups with p value 0.91.

MEAN DISTRIBUTION OF MEAN ARTERIAL PRESSURE BY GROUP

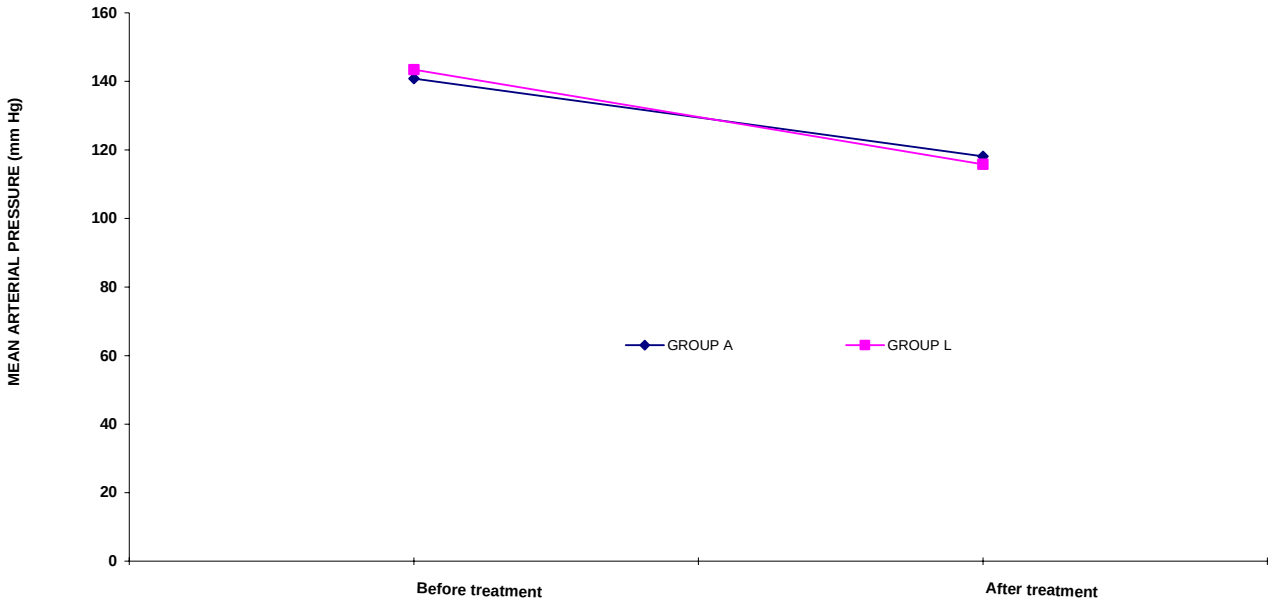


TABLE NO-10 CHANGES-MEAN ARTERIAL BLOOD PRESSURE (mm Hg)

	GROUPA(n=20)	GROUPL(n=20)	p value
BEFORE TREATMENT			
MEAN	140.8	143.4	0.51(not significant)
S.D	12.35	11.63	
	GROUPA(n=16)	GROUPL(n=19)	P value
AFTER TREATMENT			
MEAN	118.1	115.8	(0.09)(Not significant)
S.D	4.57	3.01	

Table no-10 shows the changes in mean arterial blood pressure in the 2 groups

In Group A patients (n=20) the average mean arterial blood pressure before treatment is 140.8 mmHg.

In Group L patients (n=20) the average mean blood pressure before treatment is 143.4 mmHg.

Both groups are comparable with p value (0.51) not significant.

In Group A patients (n=16) the average Mean blood pressure after treatment is118.1 mmHg.

In Group L patients (n=19) the average Mean blood pressure after treatment is 115.8 mmHg.

There is no statistical significance between the 2 Groups with p value 0.09.

MEAN DISTRIBUTION OF MATERNAL HEART RATE BY GROUP

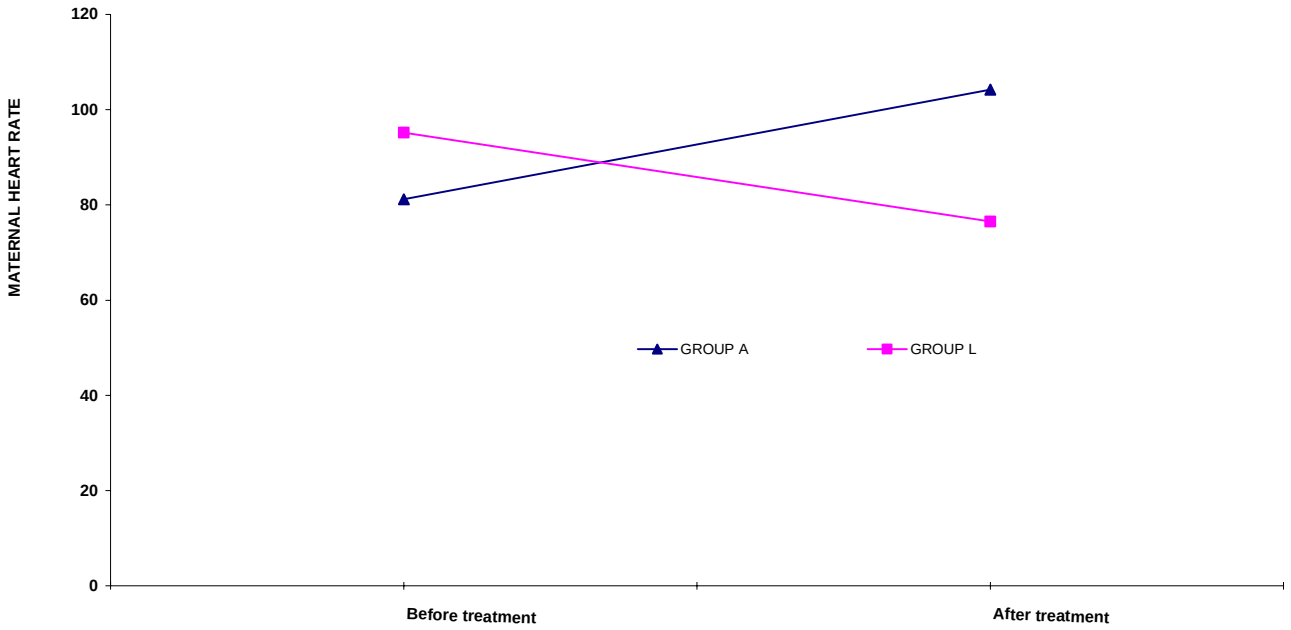


TABLE NO-11 CHANGES-MATERNAL HEART RATE (/min)

	GROUP (n=16)	GROUP (n=19)	p value
BEFORE TREATMENT			
MEAN	81.2	95.2	<0.001(significant)
S.D	7.29	6.68	
	GROUPA(n=16)	GROUPL(n=19)	P value
AFTER TREATMENT			
MEAN	104.2	76.5	<0.001(significant)
S.D	11.48	7.89	

Table no-11 shows the changes in maternal heart rate in the 2 groups

In Group A patients (n=16) the mean maternal heart rate before treatment is 81.2/min.

In Group L patients (n=19) the mean maternal heart rate before treatment is 95.2/min. Both groups are not comparable with a significant p value <0.001.

In Group A patients (n=16) the mean maternal heart rate after treatment is104.2/min. In Group L patients (n=19) the mean maternal heart rate after treatment is 76.5/min.

There is no statistical significance between the 2 Groups with p value <0.001.

However in Group A patients (n=16) the difference between the mean maternal heart rate before and after treatment is a rise of+23/min (28.32%)showing a statistically significant p value<0.001. This rise in maternal heart rate is due to the use of rescue drug injection nitroglycerin in group A patients.

In Group L patients (n=19) the difference between the mean maternal heart rate before and after treatment is a fall of-18.7/min (19.64%) showing a statistically significant p value <0.001.

MEAN DISTRIBUTION OF MATERNAL RESPIRATORY RATE BY GROUP

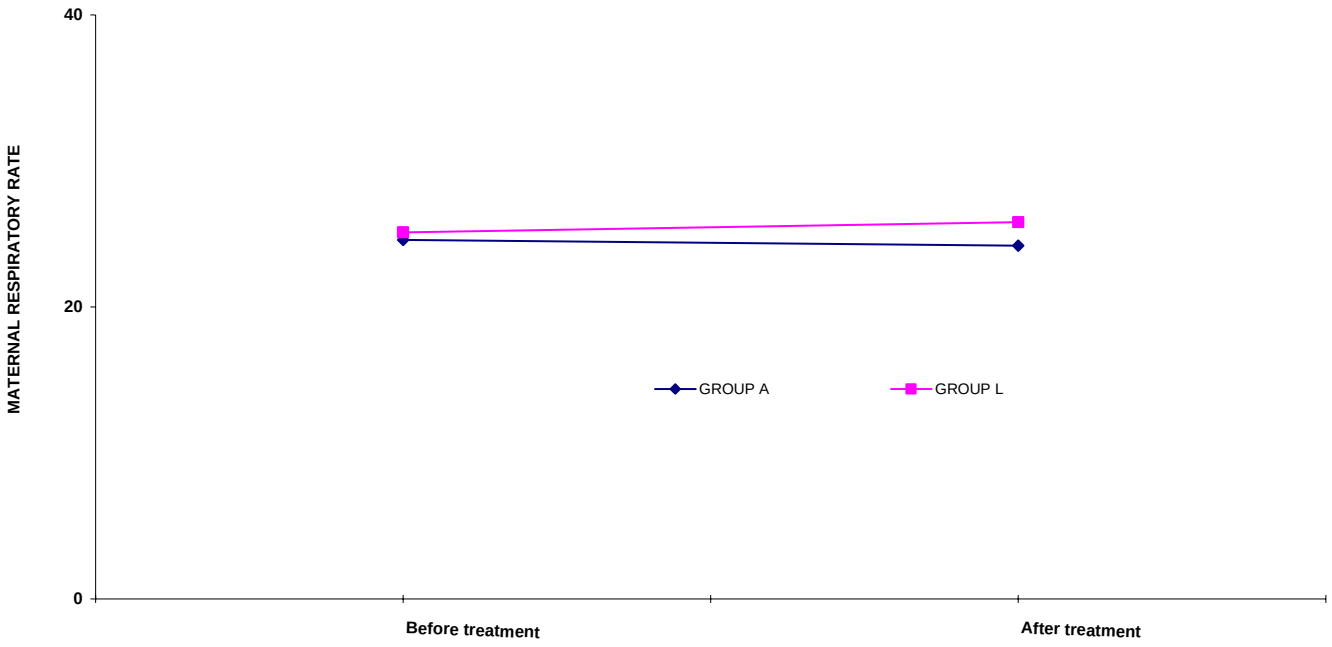


TABLE NO-12 CHANGES-MATERNAL RESPIRATORY RATE (/min)

	GROUPA(n=20)	GROUPL(n=20)	p value
BEFORE TREATMENT			
MEAN	24.6	25.1	0.55(not significant)
S.D	2-01	2.7	
	GROUP (n=16)	GROUPL(n=19)	P value
AFTER TREATMENT			
MEAN	24.4	25.8	0.05(significant)
S.D	1.09	2.71	

Table no-12 shows the changes in maternal respiratory rate in the 2 groups

In Group A patients the mean maternal respiratory rate before treatment is 24.6/min. In Group L patients the mean maternal respiratory rate before treatment is 25.1/min. Both groups are comparable with a p value 0.55 not statistically significant.

In Group A patients the mean maternal respiratory rate after treatment is 24.4/min.

In Group L patients the mean maternal respiratory rate after treatment is 25.8/min.

There is statistical difference between the 2 groups with p value0.05.

TABLE NO-13 CHANGES-MATERNAL URINE OUTPUT (ml)

	GROUPA(n=20)	GROUPL(n=20)	p value
MEAN	175.0	137.5	0.07(not significant)
S.D	59.60	65.60	

Table no-13 shows the changes in urine output the 2 groups In Group A patients the mean urine output is 175ml.In Group L patients the mean urine output is 137.5ml.There is no statistical difference between the 2 groups with p value 0.07.

MEAN DISTRIBUTION OF FETAL HEART RATE BY GROUP

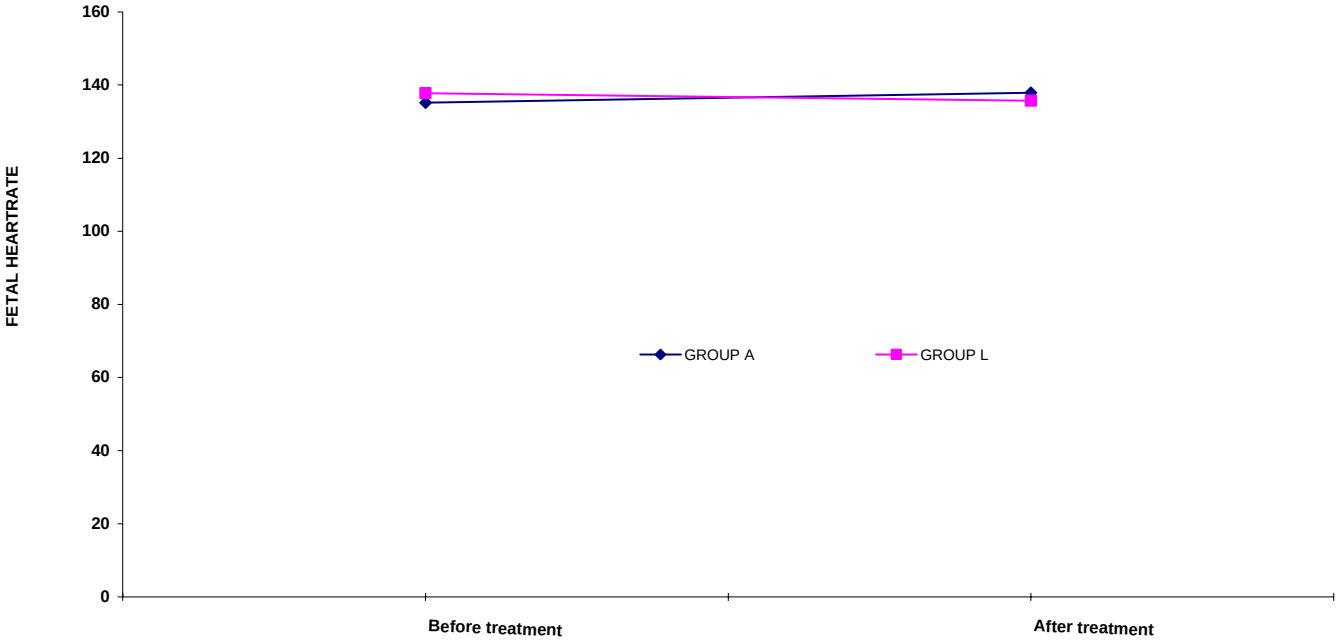


TABLE NO-14 CHANGES-FETAL HEART RATE (/min)

	GROUPA(n=20)	GROUPL(n=20)	p value
BEFORE TREATMENT			
MEAN	135.2	137.8	0.15(not significant)
S.D	4.87	6.15	
	GROUPA (n=16)	GROUPL(n=19)	P value
AFTER TREATMENT			
MEAN	137.9	135.7	0.25(not significant)
S.D	5.91	5.13	

Table no-14 shows the changes in fetal heart rate in the 2 groups. In Group A patients the mean fetal heart rate before treatment is 135.2/min. In Group L patients the mean fetal heart rate before treatment is 137.8/min. Both groups are comparable with a p value 0.15 not statistically significant. In Group A patients the mean fetal heart rate after treatment is 137.9/min. In Group L patients the mean fetal heart rate after treatment is 135.7/min.

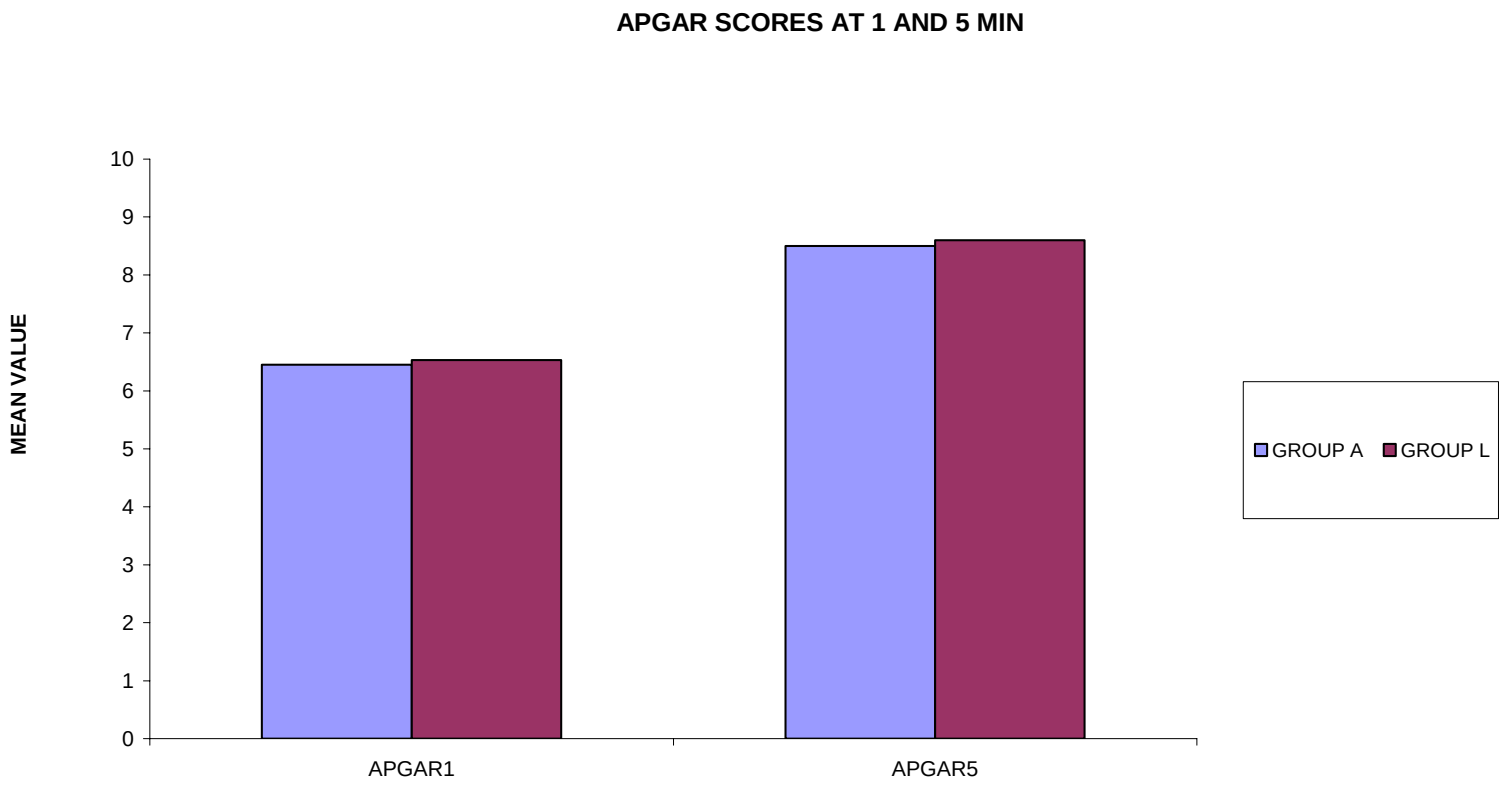
There is no statistical difference between the 2 groups with p value 0.25

TABLE NO -15 GROUP A

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	Mat HR (/min)	R.R (/min)	Fet HR(/min)	U.O (ml)	TIME (min)
BEFORE TREATMENT	178.1+/-14.34	118.7+/-12.16	140.8+/-12.35	81.2+/-7.29	24.6+/-2.01	137.8+/-6.15	175.0+/-59.60	185.9+/-20.75
AFTER TREATMENT	151.8+/-5.34	100.4+/-4.15	118.1+/-4.57	104.2+/-11.48	24.2+/-1.09	**135.7+/-5.13**		

TABLE NO- 16 GROUP L

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	Mat HR(/min)	R.R (/min)	Fet HR(/min)	U.O(ml)	TIME (min)
BEFORE TREATMENT	184.7+/-19.16	122.7+/-8.43	143.4+/-11.63	95.2+/-6.68	25.1+/-2.7	137.8+/-6.15	137.5+/-65.60	46.8+/-11.57
AFTER TREATMENT	146.2+/-4.5	100.6+/-3.42	115.8+/-3.01	76.5+/-7.89	25.8+/-2.71	**135.7+/-5.13**		


APGAR SCORES AT 1 AND 5 MIN
MEAN VALUE
10
9
8
7
6
5
4
3
2
1
0
APGAR1
APGAR5
GROUP A
GROUP L

APGAR SCORES-1 MIN &5 MIN-DISTRIBUTION TABLE

APGAR SCORE	GROUPA (n=20)	GROUPL (n=19)	p value
1 MIN			0.70(not significant)
MEAN	6.45	6.53	
S.D	0.61	0.61	
MEDIAN	6	6	
RANGE	6-8	6-8	
5 MIN			0.42(not significant)
MEAN	8.5	8.6	
S.D	0.51	0.50	
MEDIAN	8.5	9	
RANGE	8-9	8-9	

Table shows the distribution of Apgar scores of both group neonates at 1min and 5min intervals.

In group A neonates the mean Apgar at 1min is 6.45.

In group L neonates the mean Apgar at 1 min is 6.53.

Both groups are comparable with a p value of 0.70

In group A neonates the mean Apgar at 5min is 8.5.

In group L neonates the mean Apgar at 5 min is 8.6.

Both groups are comparable with a p value of 0.42.

DISCUSSION

In severe Pregnancy induced hypertension patients it is of vital importance to control high blood pressure preoperatively to reduce the incidence of maternal complications like pulmonary edema, intracerebral hemorrhage and renal failure. Fetal complications include intra uterine growth retardation (IUGR), perinatal mortality.

Various drugs like methyldopa, ketanserin, hydralizine, labetalol, nifedipine have been used to control high blood pressure.

Montan, Sven et al A in their prospective study before and after 1 week of methyldopa treatment observed that Maternal mean arterial blood pressure was reduced 9.7 mm Hg (95% confidence interval -13.8 to -5.6) from (114.5+/_6.1mmHg to 104.8+/_6.2 mmHg), and mean heart rate decreased 6.3 beats/min (95% confidence interval -11.1 to -1.4)(from90.0+/_ to83.7+/-11.8). Fetal hemodynamic changes before and after treatment were not significant. Fetal and neonatal outcome was uneventful.(18)

In our study group A patients were administered a combination of oral alpha methyldopa and nifedipine. Only 16 out of 20 patients achieved blood pressure control and 4 patients failed to achieve target blood pressure despite using intravenous nitro glycerin as rescue drug. Also out of the 16 patients who achieved blood pressure control 13 patients necessitated the use of rescue drug namely intravenous nitroglycerin. Only 3 patients achieved blood pressure control within 3 hours after starting oral antihypertensive combination without use of rescue drug nitroglycerin. The maternal mean arterial blood pressure was reduced 22.7mmHg

from 140.8+/-12.35mmHg to 118.1+/-mmHg and but mean maternal heart rate increased 23/min from 81.2+/-7.29/min to 104.2+/-11.48/min due to nitroglycerin induced reflex tachycardia.

In our study group L patients were administered intravenous labetalol. 19 out of 20 patients achieved blood pressure control with one patient failing to do so. In that patient the dose was restricted to a maximum of 2mgm/kg, though a maximum of 220 mgm per episode has been recommended. The maternal mean arterial blood pressure was reduced 27.4mmHg from 143.4+/- 11.63mmHg to 115.8+/-3.01mmHg while the mean maternal heart rate was reduced 18.7/min from 95.2+/-6.68/min to 76.5+/-7.89/min. Since Injection labetalol 20 mgm was administered intravenously and repeated every 10 minutes if necessary with careful monitoring, there was not any case of hypotension or hemodynamic collapse. One patient delivered a dead born baby .One of the known fetal complications of severe pregnancy induced hypertension is perinatal mortality due to uncontrolled hypertension.

In our study Group L patients target blood pressure was achieved in a shorter time of 46.8+/-11.57min when compared to group A patients who took a longer time of 185.9+/-20.75min.

In our study group L patients who received intravenous Labetalol for acute preoperative management of high blood pressure in severe Pregnancy Induced Hypertension (PIH) achieved more rapid blood pressure control with better heart rate control than Group A patients who received oral antihypertensives.

SUMMARY

Comparative clinical study of acute preoperative management of high blood pressure in severe pregnancy induced hypertension patients using two methods: one by (group A) an oral combination of tablets Alphamethyldopa and Nifedepine and other by (group L) intravenous Labetalol was undertaken at the Institute of Obstetrics and Gynaecology,Madras medical college & research institute, Chennai during the year 2006-2008. Summarizing the findings in the study:

1.Oral antihypertensive combination of tablets Alphamethyldopa and Nifedepine achieved blood pressure control that often necessitated intravenous Nitroglycerin as rescue drug.

2.Intravenous Labetalol achieves adequate and faster blood pressure control with better heart rate maintenance than the routinely used oral antihypertensive combination

CONCLUSION

In conclusion, intravenous Labetalol achieves adequete and faster blood pressure control with better heart rate maintenance than the routinely used oral antihypertensive combination of tablets Alphamethyldopa and Nifedipine in the control of blood pressure in preoperative severe pregnancy induced hypertension patients.

BIBLIOGRAPHY

1) Andre van Zundert;Gerard W. Ostheimer;Pain Releif and Anesthesia in Obstetrics, 1996

2) Belfort MA, Tooke-Miller C, Allen JC Jr, Dizon-Townson D, Varner MA.Labetalol decreases cerebral perfusion pressure without negatively affecting cerebral blood flow in hypertensive gravidas. 4: Hypertens Pregnancy. 2002;21(3):185-97.

3) Birnbach DJ,Gatt SP,Datta S (eds):Textbook of Obstetric anesthesia,New york,Churchill Livingstone,2000,p543.

4) Carl P.Weiner;Catalin Buhimschi,Drugs For Pregnant And Lactating Women,2004.

5) Chung KS, Sinatra RS, Chung JH. The effect of an intermediate dose of labetalol on heart rate and blood pressure responses to laryngoscopy and intubation. J Clin Anesth. 1992 Jan-Feb;4(1):11-5.

6) Connell H, Dalgleish JG, Downing JW. General anaesthesia in mothers with severe pre-eclampsia/eclampsia. : Br J Anaesth. 1987 Nov;59(11):1375-80.

7) David H.Chestnut Obstetric Anesthesia Principles &Practice Third Edition 2004.

8) El-Qarmalawi AM, Morsy AH, al-Fadly A, Obeid A, Hashem M.Labetalol vs. methyldopa in the treatment of pregnancy-induced hypertension. Int J Gynaecol Obstet. 1995 May;49(2):125-30

9) F.Gary Cunningham,KennathJ.Leveno;Steven L. Bloom;Williams Obstetrics.22nd Edition.2005.

10) Gerald G .Briggs;Roger K. Freeman;Drugs In Pregnancy And Lactation;Seventh Edition2005.
11) Gilson GJ, Kramer RL, Barada C, Izquierdo LA, Curet LB. Does labetalol Gilson GJ, Kramer RL, Barada C, Izquierdo LA, Curet LB. Does labetalol
12) Joel G.Hardman;Lee E.Limbird;Goodman &Gillmans The Pharmacologic Basis of Therapeutics Tenth Edition 2001.
13) Kumar N, Batra YK, Bala I, Gopalan S. Nifedipine attenuates the hypertensive response to tracheal intubation in pregnancy-induced hypertension. : Can J Anaesth. 1993 Apr;40(4):329-33.
14) Kwawukume EY, Ghosh TS. Oral nifedipine therapy in the management of severe preeclampsia Int J Gynaecol Obstet. 1995 Jun;49(3):265-9.
15) Lee SC, Fung ST, Lee JH [Effects of labetalol and nitroglycerin during induction of anesthesia and endotracheal intubation in hypertensive patients] : Ma Zui Xue Za Zhi. 1989 Sep;27(3):247-54.
16) Leslie JB, Kalayjian RW, McLoughlin TM, Plachetka JR. Attenuation of the hemodynamic responses to endotracheal intubation with preinduction intravenous labetalol. : J Clin Anesth. 1989;1(3):194-200.
17) Mahmoud TZ, Bjornsson S, Calder AA. Labetalol therapy in pregnancy induced hypertension: the effects on fetoplacental circulation and fetal outcome. : Eur J Obstet Gynecol Reprod Biol. 1993 Jul;50(2):109-13.
18) Montan, Sven; Anandakumar, Chinnaiya; Arulkumaran, Sabaratnam; Ingemarsson, Ingemar; Ratnam, Shan S. Effects of Methyldopa on Uteroplacental and Fetal Hemodynamics in Pregnancy-Induced Hypertension. American Journal of Obstetrics & Gynecology. 168(1):152-156, January 1993.
19) Olsen KS, Beier-Holgersen R. Fetal death following labetalol administration in pre-eclampsia. Acta Obstet Gynecol Scand. 1992 Feb;71(2):145-7.

20) Olsen KS, Beier-Holgersen R.Hemodynamic collapse following labetalol administration in pre-eclampsia. Acta Obstet Gynecol Scand. 1992 Feb;71(2):151-2.

21) Ramanathan J, Coleman P, Sibai B.Anesthetic modification of hemodynamic and neuroendocrine stress responses to cesarean delivery in women with severe preeclampsia. Anesth Analg. 1991 Dec;73(6):772-9.

22) Robert K Stoelting Third edition,1999 Page 344-347 Pharmacology and physiology in anestheic practice.

23) Ronald D Miller,Miller s Anesthesia,sixth edition.p2307-2344.

24) Scardo, James A. MD a; Vermillion, Stephen T. MD b; Newman, Roger B. MD b; Chauhan, Suneet P. MD a; Hogg, Barbara B. MD b randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. American Journal of Obstetrics & Gynecology. 181(4):862-866, October 1999.

25) Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia - a state of sympathetic overactivity. : N Engl J Med. 1996 Nov 14;335(20):1480-5.

26) Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, Lopez JC;or the HYLA treatment study. Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. 1: Eur J Obstet Gynecol Reprod Biol. 2006 Sep-Oct;128(1-2):157-62.

27) Wallace DH, Leveno KJ, Cunningham FG, Giesecke AH, Shearer VE, SidawiJE. Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. : Obstet Gynecol. 1995 Aug;86(2):193-9.

PROFORMA

NAME : AGE : HOSP NO:

OBSTETRICS H/O : BOOKED /UNBOOKED

HISTORY C/O :

H/o. PRESENTING ILLNESS :

1. HEADACHE
2. VISUAL DISTURBANCE
3. RIGHT UPPER QUADRANT PAIN
4. OLIGURIA
5. FITS
6. EDEMA
7. ABNORMAL BLEEDING
8. LAST VOIDING URINE
9. MEMBRANES RUPTURED
10. PAIN ABDOMEN
11. NPO STATUS

H/o. PAST ILLENSS :

1. HYPERTENSION
2. DIABETESMELLITUS.
3. BRONCHIALASTHMA.
4. SEXUALLY TRANSMITTED DISEASES
5. RHEUMATIC HEART DISEASE
6. JAUNDICE
7. PREVIOUS SURGERY

TREATMENT H/O. :

ANTIHYPERSIVE DRUGS

ALLERGY

GENERAL EXAMINATION :

- CONSCIOUS - ORIENTED - COMFORTABLE / PAIN / DYSPNOEIC - PALLOR - JAUNDICE - CLUBBING - CYANOSIS - EDEMA - SIGNIFICANT GENERALIZED LYMPHADENOPATHY - HYDRATION - HEIGHT WEIGHT - BMI - H.R.	- B.P. - R.R. - TEMP. - JVP - SP02 - BREAST & THYROID - SPINES - AIRWAY ▪ MOUTH OPENING ▪ MPC ▪ THYROMENTAL DISTANCE ▪ ANY DIFF.

SYSTEMIC EXAM.

1. C.V.S.
2. R.S.
3. CNS
4. ABDOMEN

INVESTIGATIONS

HB	URINE
BLOOD GROUP	RH TYPE
UREA	CREATININE
ELECTROLYTES	URIC ACID
SUGAR	FIBRINOGEN
CLOTTING TIME	BLEEDING TIME

EVENTS	TIME	SYSTOLIC BP	DIASTBP	MAP Mm/ Hg	HR/ Min	Sp02 %	RR/ Min	UO Ml/ Hr	FHR/min
ON ADMISSION									
ORAL/IV ANTIHYPERENSIVE START ED									
BLOOD PRESSURE TARGET ACHIEVED/FAILED									
TIME TAKEN (MIN)									

GROUP - A

TIME IN MINUTES AFTER STARTING TREATMENT

SYSTOLIC BLOOD PRESSURE (mm Hg) **DIASTOLIC BLOOD PRESS**

	0	20	40	60	80	100	120	140	160	180	185	190	195	200	205	210	215	220	225	230	235	240	245	250	255	0	20	40	60	80	100	120	140	160	180	185	190	195	200	20
1	186	167	167	176	172	162	176	170	161	192	187	177	181	179	169	163	167	171	163	171						132	113	117	122	126	118	106	110	109	133	127	123	127	131	12
2	170	167	167	161	157	162	161	159	167	168	158	159	161	153												110	113	117	119	112	118	107	111	119	112	110	123	109	104		
3	196	188	178	182	178	167	172	168	186	186	176	158	154	153												112	116	112	113	120	118	113	111	123	108	106	102	103	104		
4	176	167	171	173	169	165	159	159	165	172	163	161	159	153	149											108	111	113	122	117	109	115	121	117	109	107	107	100	101	97
5	168	166	158	162	159	171	169	163	161	166	152	154	148													109	111	109	112	109	113	115	111	107	107	92	94	91			
6	163	159	171	163	161	159	161	160	159	161	158	136	138	143	140											117	119	121	113	114	109	107	110	107	107	106	88	91	96	92
7	208	201	197	188	178	189	181	183	181	192	186	179	167	159	153	149										146	136	122	132	133	123	119	121	117	132	122	123	119	111	10
8	166	158	171	165	164	167	172	171	168	172	160	146														106	108	106	109	112	114	108	109	113	111	108	102				
9	212	198	211	188	179	192	197	192	194	208	188	186	179	180	178	179	173	183	179							146	138	126	132	126	132	119	122	126	132	137	135	130	126	12
10	186	192	187	177	182	179	183	191	179	192	179	181	176	172	169	176	180	176	169	176	180	176	180	176	170	132	122	119	123	122	110	114	116	123	127	129	123	127	122	11
11	186	176	171	168	159	162	165	172	168	178	166	168	160													120	118	113	109	119	120	117	110	106	110	108	109	104			
12	166	162	158	170	162	158	156	158	148																	110	108	112	108	110	107	106	106	100							
13	176	159	161	166	170	162	158	162	164	154																108	117	112	108	109	110	108	113	110	102						
14	160	166	172	171	167	162	168	170	172	158	149	150	148													112	118	119	118	115	109	110	112	108	112	103	102	93			
15	176	171	178	162	164	160	157	162	160	166	166	162	158	152												123	119	112	109	110	110	113	110	106	108	106	106	111	104		
16	166	162	168	171	168	166	158	156	164	158	162	166	164	162	158	162	156									126	122	119	130	115	112	108	118	124	128	126	118	117	121	11
17	176	164	160	166	158	178	170	167	182	168	158	156	158													112	110	110	112	110	110	109	113	108	106	102					
18	176	172	179	170	163	167	165	174	182	168	162	156														108	112	119	110	107	106	107	108	110	104	106	98				
19	183	176	177	176	178	166	158																			119	113	109	110	114	108	101									
20	166	162	171	167	170	166	167	163	169	161	159	167	158	157												117	113	113	109	110	117	111	112	121	115	111	109	107	103		

GROUP - A

TIME IN MINUTES AFTER STARTING TREATMENT

MEAN ARTERIAL PRESSURE (mmHg)

	0	20	40	60	80	100	120	140	160	180	185	190	195	200	205	210	215	220	225	230	235	240	245	250	255
1	150	131	134	140	141	133	129	130	126	153	147	141	145	147	137	132	128	131	125	132					
2	100	94	134	113	121	133	126	127	135	131	126	128	126	120											
3	140	106	134	122	139	134	133	128	132	138.3	129	121													
4	131	130	132	119	134	128	130	134	133	135.9	126	123	120												
5	129	129	125	129	126	132	131	128	133	127	112														
6	132	132	138	130	130	126	131	127	124	130	124	104													
7	167	158	134	151	129	128	140	142	138	152	143	142	135	127	124	119									
8	155	125	128	128	129	131	129	130	131	131	125	117													
9	159	136	154	151	144	130	133	145	149	157	131	125	146	144	142	144	138	146	139						
10	158	145	142	143	139	130	131	140	142	149	146	142	143	139	136	143	141	143	136	143	141	143	141	146	140
11	158	137	132	129	132	130	132	131	127	133	127	129	123												
12	129	140	127	129	127	130	123	123	116																
13	131	139	128	127	129	127	125	129	120	119															
14	130	139	137	136	132	127	129	131	129	127	118														
15	141	136	134	127	131	127	127	127	126	127	79	125	127	121											
16	139	135	135	144	133	127	125	131	137	127	138	134	133	134	132	131	132								
17	133	135	127	138	132	133	129	130	133	127	121														
18	131	135	130	140	126	126	126	130	134	126	125	117													
19	140	135	132	140	135	127	120																		
20	133	129	132	128	132	133	130	129	137	130	127	126	124	121											

MATERNAL HEART RATE (per min)

	0	20	40	60	80	100	120	140	160	180	185	190	195	200	205	210	215	22
1	87	73	76	78	77	73	78	79	83	74	79	81	82	84	81	87	83	86
2	87	85	87	89	91	88	87	89	93	93	106	109	111	117				
3	81	82	86	87	85	89	87	89	91	89	107	113						
4	76	77	79	83	82	86	82	81	89	83	93	109	117					
5	68	71	73	74	72	77	76	69	77	79	97							
6	79	83	81	84	85	85	84	83	79	79	93	99						
7	67	69	68	71	73	74	71	77	78	77	90	93	101	102	103	107		
8	82	81	83	87	83	84	84	83	83	81	93	97						
9	101	88	88	86	87	91	88	87	88	89	104	99	99	103	100	96	89	93
10	91	85	83	89	87	83	89	87	91	98	83	91	89	86	81	87	91	89
11	92	88	93	91	87	88	87	84	85	87	97	109	111					
12	81	83	84	87	91	88	89	90	89									
13	76	78	82	83	81	84	85	83	87	86								
14	86	88	84	89	84	88	89	92	92	91	102							
15	87	88	82	87	84	86	91	87	82	89	107	110	113	117				
16	91	89	89	92	90	88	92	93	94	93	97	100	99	100	101	98	101	
17	90	88	89	88	86	91	90	89	96	95	107							
18	88	87	86	89	90	88	89	90	96	93	112	118						
19	76	77	78	81	82	87	83											
20	83	87	84	86	90	87	89	90	86	88	106	99	101	107				

GROUP - A
TIME IN MINUTES AFTER STARTING TREATMENT

	RESPIRATORY RATE (per min)																										URINE OUTPUT (ml)
	0	20	40	60	80	100	120	140	160	180	185	190	195	200	205	210	215	220	225	230	235	240	245	250	255		0
1	31	30	28	29	28	29	30	28	29	27	28	28	29	30	27	28	29	28	28	29							50
2	24	23	24	23	25	23	25	23	25	23	24	24	25	23	24	25											150
3	24	23	24	25	26	24	23	24	25	26	24	25	22	24													100
4	23	21	22	24	25	23	21	23	24	21	23	22	23	24	23												150
5	26	24	24	23	26	23	25	26	25	23	23	25	24														200
6	26	23	26	23	25	26	25	23	23	25	24	25	24	21	23												200
7	23	21	22	24	25	23	21	23	24	21	23	22	23	24	23												200
8	23	26	23	25	26	25	23	23	25	24	25	24	21	23	24												200
9	23	26	23	25	26	25	23	23	25	24	25	24	21	23	24	23	24	26	25								250
10	23	26	23	25	26	25	23	23	25	24	25	24	21	23	24	23	25	24	25	24	21	23	24	23	24		150
11	23	26	23	25	26	25	23	23	25	24	25	24	21	23	24												200
12	26	23	25	26	25	23	23	25	24	25	24																200
13	23	26	23	25	26	25	23	23	25	24	25	24															150
14	26	23	25	26	25	23	23	25	24	25	24	23	25														200
15	23	26	23	25	26	25	23	23	25	24	25	24	21	23	23	24	26										150
16	26	23	25	26	25	23	23	25	24	25	24	23	25	24	27	25	26										200
17	23	25	26	25	23	23	25	24	25	24	23	25	27														300
18	25	26	25	23	23	25	24	25	24	23	25	24	27	25													250
19	25	24	25	24	23	25	24	27	25																		100
20	26	25	23	23	25	24	25	24	23	25	24	27	25	27	23	24											100

GROUP - A
TIME IN MINUTES AFTER STARTING TREATMENT

	FETAL HEART RATE (per min)																									PULSE OXIME												
	0	20	40	60	80	100	120	140	160	180	185	190	195	200	205	210	215	220	225	230	235	240	245	250	255	0	20	40	60	80	100	120	140	160	180	185	190	195	200
1	132	138	132	144	138	132	138	132	138	126	144	138	132	138	132	144	138	144	138	132						99	99	99	99	99	99	99	99	99	99	99	99	99	99
2	132	134	144	124	134	144	136	134	134	142	144	136	142	140	128	132										99	99	99	99	99	99	99	99	99	99	99	99	99	99
3	132	132	138	132	144	138	132	138	132	138	126	144	138	132												99	99	99	99	99	99	99	99	99	99	99	99	99	99
4	132	138	132	144	138	132	138	132	138	126	144	138	132	134	132											99	99	99	99	99	99	99	99	99	99	99	99	99	99
5	134	134	144	124	134	144	136	134	134	142	144	136	142													99	99	99	99	99	99	99	99	99	99	99	99	99	
6	132	144	138	132	138	132	138	126	144	138	132	134	132													99	99	99	99	99	99	99	99	99	99	99	99	99	
7	132	138	132	144	138	132	138	132	138	126	144	138	132	134	132	144	136	142								99	99	99	99	99	99	99	99	99	99	99	99	99	99
8	134	144	124	134	144	136	134	134	142	144	136	142	138	126	144											99	99	99	99	99	99	99	99	99	99	99	99	99	99
9	132	144	138	132	138	132	138	126	144	138	132	134	132	144	136	142	138	126	144							99	99	99	99	99	99	99	99	99	99	99	99	99	99
10	132	144	138	132	138	132	138	126	144	138	132	134	132	144	136	142	138	126	144	136	142	138	126	144	138	99	99	99	99	99	99	99	99	99	99	99	99	99	99
11	144	138	132	138	132	138	126	144	138	132	134	132	144	136	142											99	99	99	99	99	99	99	99	99	99	99	99	99	99
12	132	138	132	138	126	144	138	132	134	132	144															99	99	99	99	99	99	99	99	99	99	99			
13	144	138	132	138	132	138	126	144	138	132	134	132														99	99	99	99	99	99	99	99	99	99	99	99		
14	144	138	132	138	132	138	126	144	138	132	134	132	144													99	99	99	99	99	99	99	99	99	99	99	99	99	
15	138	132	138	132	138	126	144	138	132	134	132	136	138	134	138	144	128									99	99	99	99	99	99	99	99	99	99	99	99	99	99
16	132	138	132	138	126	144	138	132	134	132	136	138	134	138	144	128	140									99	99	99	99	99	99	99	99	99	99	99	99	99	99
17	132	138	126	144	138	132	134	132	136	138	134	138	144													99	99	99	99	99	99	99	99	99	99	99	99	99	
18	144	138	132	138	132	138	126	144	138	132	134	132	144	138												99	99	99	99	99	99	99	99	99	99	99	99	99	99
19	132	138	132	138	126	144	138	132	134																	99	99	99	99	99	99	99	99	99	99				
20	138	132	138	132	138	126	144	138	132	134	132	144	138	132	138	144										99	99	99	99	99	99	99	99	99	99	99	99	99	99

GROUP - L
TIME IN MINUTES AFTER STARTING TREATMENT

SYSTOLIC BLOOD PRESSURE (mm Hg)

A	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
1	200	190	164	144	140	142	146	142															
2	160	161	158	156	161	158	153	156	153	146	141	143											
3	166	172	171	170	168	167	171	173	167	161	158	158	141	142									
4	176	183	181	179	177	181	172	171	171	168	171	167	153	143									
5	166	172	166	158	161	151	146																
6	186	190	182	183	172	177	176	171	168	158	161	153	147	141									
7	200	240	230	200	210	220	210	220	206	200	186	210	180	170	200	210	206	212	198	200	186	180	206
8	176	182	179	177	168	169	163	158	156	156	148												
9	186	182	176	178	170	166	160	159	163	161	158	157	151	151									
10	176	179	177	182	179	169	171	168	160	159	158	156											
11	176	182	187	170	179	169	177	163	159	161	154	153	151	149									
12	168	176	172	168	163	168	159	156	152	156	152												
13	200	201	195	189	176	162	169	173	166	159	153												
14	162	160	158	156	158	151	146																
15	196	202	196	176	172	169	167	171	163	158	146												
16	220	216	198	190	177	182	170	168	161	158	163	151	143										
17	162	164	159	163	161	157	153	151	149														
18	176	178	171	169	162	164	158	163	159	157	153	146											
19	166	172	169	163	159	160	158	153	146	141													
20	186	192	187	183	176	173	163	169	158	156	149	141											

DIASTOLIC BLOOD PRESSURE

A	0	5	10	15	20	25	30	35	40	45	50	55	60	65
1	120	132	126	111	111	112	108	101						
2	120	119	116	117	117	113	111	110	113	109	107	103		
3	114	118	121	123	121	119	117	119	119	117	113	116	107	102
4	118	123	127	125	123	124	121	121	118	121	117	119	111	101
5	107	114	109	111	102	106	99							
6	112	122	120	117	121	123	117	118	112	111	107	111	109	92
7	130	140	140	140	140	140	136	140	138	140	136	140	126	126
8	110	116	113	111	120	109	111	109	106	109	102			
9	126	123	120	118	112	108	109	113	111	109	113	106	106	101
10	116	122	111	114	113	111	109	107	109	111	109	101		
11	116	122	123	114	113	117	111	113	115	113	107	109	106	101
12	112	118	119	116	121	112	109	111	108	112	101			
13	141	136	119	121	132	126	122	117	109	106	101			
14	112	108	109	112	109	111	104							
15	130	128	123	126	121	119	113	109	107	113	104			
16	140	132	128	131	122	118	113	117	121	117	109	106	102	
17	112	114	116	109	107	109	111	107	101					
18	116	122	119	121	118	112	109	107	105	107	109	101		
19	108	112	113	109	113	111	107	111	106	91				
20	126	132	121	119	112	119	117	111	109	111	106	103		

GROUP - L
TIME IN MINUTES AFTER STARTING TREATMENT

MEAN ARTERIAL PRESSURE (mmHg)

	A	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
1	147	151	139	122	121	122	121	115																
2	133	133	130	130	132	128	125	125	126	121	118	116												
3	131	136	138	139	137	135	135	137	135	132	128	130	118	115										
4	137	143	145	143	141	143	138	138	136	137	135	135	125	115										
5	127	133	128	127	122	121	115																	
6	137	145	141	139	138	141	137	136	131	127	125	125	122	108										
7	153	173	170	160	163	167	161	167	161	160	153	163	145	142	153	161	161	155	145	145	141	147	157	
8	132	138	135	133	136	129	128	125	123	125	117													
9	147	143	139	138	131	127	126	128	128	126	128	123	121	118										
10	136	141	133	137	135	130	130	127	126	127	125	119												
11	136	142	144	133	135	134	133	130	130	129	123	124	121	118										
12	131	137	137	133	135	131	126	126	123	130	118													
13	161	158	144	144	147	139	138	136	128	124	118													
14	128	125	125	130	125	124	118																	
15	152	153	147	143	138	136	131	130	126	128	118													
16	167	160	151	151	140	139	132	134	134	131	127	121	116											
17	129	131	130	127	125	125	125	122	117															
18	136	141	136	137	133	129	125	126	123	124	124	116												
19	127	132	132	127	128	127	124	125	119	108														
20	147	152	143	140	133	137	132	130	125	126	120	116												

MATERNAL HEART RATE (per m

	A	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70
1	96	91	92	93	86	87	86	84								
2	108	101	108	106	102	100	101	97	99	96	92	87				
3	89	98	97	96	93	91	87	81	83	81	83	82	78	77		
4	112	101	115	111	109	107	103	101	99	93	96	95	91	87		
5	82	81	79	77	75	71	71									
6	96	97	95	91	89	87	85	87	83	85	81	79	77	75		
7	86	84	83	82	84	85	86	86	82	77	82	81	81	84	85	85
8	86	92	90	86	85	84	83	81	79	79	77					
9	146	103	124	116	108	102	98	93	91	87	89	87	85	85		
10	110	101	109	101	96	94	91	94	88	87	83	81				
11	99	97	90	77	71	69	67	71	71	69	66	67	66	67		
12	86	91	89	86	87	83	81	83	81	83	84					
13	96	97	93	97	95	91	92	87	86	81	79					
14	96	99	96	92	90	88	82									
15	96	99	93	91	87	85	81	83	81	83	80					
16	77	79	78	77	75	77	73	77	75	71	70	66	61			
17	82	89	87	82	84	80	79	77	75							
18	96	98	90	88	81	79	77	79	77	75	73	69				
19	89	93	89	85	81	79	77	71	69	63						
20	112	101	108	96	90	93	86	81	77	79	71	70				

GROUP - L
TIME IN MINUTES AFTER STARTING TREATMENT

RESPIRATORY RATE (per min)

	A	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
1	24	23	22	23	21	22	23	22	23	21														
2	23	22	22	21	23	23	23	21	22	23	23	23	21	23										
3	27	27	26	25	27	26	25	25	25	25	25	25	26	26	26	27								
4	22	21	20	21	25	23	22	21	23	24	21	21	22	23	22	23								
5	21	21	21	22	21	20	21	20	20	21														
6	23	24	24	23	24	25	23	22	23	24	23	23	23	23	23	22								
7	23	24	23	24	23	21	24	25	25	25	26	25	25	23	24	25	24	24	25	24	24	23	24	
8	24	23	24	22	23	24	23	24	23	24	23	24	24											
9	22	23	24	23	22	23	27	26	25	24	24	23	24	24	26									
10	26	25	26	27	28	26	25	26	25	25	24	24	25	28										
11	27	26	25	27	26	25	25	26	27	27	28	26	27	28	27	26								
12	26	27	26	25	27	28	27	26	27	26	27	26												
13	27	28	27	28	29	27	28	27	28	27	26	27	28											
14	27	25	27	24	26	27	27	26																
15	24	23	27	26	26	25	27	27	28	29	26	28												
16	28	27	28	29	30	29	29	28	26	25	27	28	29	29										
17	29	30	31	30	25	27	29	29	27	28														
18	28	29	27	26	27	28	29	29	30	29	29	30	29											
19	25	24	25	26	27	26	29	28	29	28	27													
20	28	29	30	31	29	29	28	29	29	28	29	30	29											

GROUP - L
TIME IN MINUTES AFTER STARTING TREATMENT

FETAL HEART RATE (per min)

A	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
1	145	126	144	139	147	130	126	150	149	135													
2	134	139	144	126	149	147	138	128	144	146	137	132	133	149									
3	144	148	139	149	145	135	138	145	138	133	129	142	133	129	139	132							
4	133	138	129	126	132	133	128	136	141	143	129	134	137	140	136	128							
5	126	130	135	129	135	140	139	137	133	130													
6	126	135	130	133	134	139	144	140	138	133	143	130	129	135	136	129	135						
7	140	144	148	140	136	132	130	132	130	132	130	134	132	137	136	134	136	133	136	132	128	129	131
8	136	132	136	142	140	136	135	132	131	128	134	136	138	138									
9	135	134	132	133	136	134	138	142	136	135	134	133	139	139	140								
10	135	141	137	139	142	141	142	132	137	136	137	150	143	136	138								
11	134	142	136	134	135	136	137	138	135	134	141	143	147	141	136	137	139	136					
12	138	146	142	130	137	132	136	132	136	143	142	140											
13	136	138	136	142	141	137	136	140	142	136	142	137	132										
14	136	138	137	135	136	132	138	136															
15	134	138	140	137	138	135	138	140	142	136	139	139											
16	137	135	140	132	136	140	136	137	135	139	136	138	131	136									
17	136	132	136	144	138	132	144	144	138	132													
18	138	150	144	138	132	138	132	150	144	132	138	132	126										
19	132	138	144	138	132	126	126	132	138	132	138												
20	138	132	126	138	132	138	144	138	132	138	138	132	138										

PULSE OXIMETRY (%

A	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70
1	99	99	99	99	99	99	99	99	99	99					
2	99	99	99	99	99	99	99	99	99	99	99	99	99		
3	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
4	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
5	99	99	99	99	99	99	99	99	99	99					
6	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
7	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
8	99	99	99	99	99	99	99	99	99	99	99	99	99		
9	99	99	99	99	99	99	99	99	99	99	99	99	99	99	
10	99	99	99	99	99	99	99	99	99	99	99	99	99	99	
11	99	99	99	99	99	99	99	99	99	99	99	99	99	99	
12	99	99	99	99	99	99	99	99	99	99	99				
13	99	99	99	99	99	99	99	99	99	99	99	99			
14	99	99	99	99	99	99	99								
15	99	99	99	99	99	99	99	99	99	99	99				
16	99	99	99	99	99	99	99	99	99	99	99	99	99		
17	99	99	99	99	99	99	99	99	99	99					
18	99	99	99	99	99	99	99	99	99	99	99	99			
19	99	99	99	99	99	99	99	99	99	99	99				
20	99	99	99	99	99	99	99	99	99	99	99	99			